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Menopause in women with multiple sclerosis: A systematic review

Vasilios Karageorgiou[a,*], Irene Lambrinoudaki[b], Dimitrios G. Goulis[c]

[a] 2nd Department of Psychiatry, Medical School, National and Kapodistrian University of Athens, Athens, Greece
[b] 2nd Department of Obstetrics and Gynecology, Medical School, National and Kapodistrian University of Athens, Athens, Greece
[c] Unit of Reproductive Endocrinology, 1st Department of Obstetrics and Gynecology, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece

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ABSTRACT

Aim: Sex hormones have been suggested to have neuroprotective effects in the natural history of multiple sclerosis (MS), particularly in animal studies. The aim of the present review was to retrieve and systematically synthesize the evidence on the effect of menopause and hormonal replacement treatment (HRT) on the course of MS.

Methods: A systematic literature search was conducted in the databases MEDLINE (accessed through PubMed), Scopus, clinicaltrials.gov and Cochrane Controlled Register of Trials (CENTRAL). Eligible studies were all those that included women with MS and reported on at least one of the following: a) disability and MS relapse rate before and after menopause, b) serum sex hormone concentrations, c) sexual function, d) age at menopause onset. Effects of HRT on MS clinical outcomes were also assessed.

Results: Of the 4,102 retrieved studies, 28 were included in the systematic review. Of these, one reported the age at menopause for both controls and women with MS and found no difference between the two groups. There was no difference in the rates of relapse before and after menopause (risk ratio 1.21, 95 % confidence interval 0.91–1.61, p = 0.218). Two intervention studies reported beneficial effects of estrogen therapy on women with MS; however, the majority of women were premenopausal. Three studies addressed the issue of sexual dysfunction in women with MS, but information on hormonal parameters was limited.

Conclusions: The age at menopause is not associated with the presence of MS. The evidence on a potential causal effect of estrogen depletion on disability is inconclusive; still, relapse rate seems not be associated with menopause. The effect of HRT on the natural course of the disease remains to be defined.

1. Introduction

1.1. Rationale

Multiple sclerosis (MS) is a disease of the central nervous system, characterized by hallmark lesions of immunologically triggered demyelination. The process results in plaque formation, the neuroanatomical distribution of which leads to the individual symptomatology. A ubiquitous finding in epidemiological studies is the increased prevalence of MS in women compared with men [1], with further indications of a widening of the sex difference, attributed to environmental changes [2]. Evidence on sex differences in the transition to secondary progressive MS is conflicting ([3]; Tremlett et al., 2008). Of interest, the age of onset of MS has been positively correlated with the age at menarche, in a questionnaire-based study of 200 women with MS [4].

The interplay between MS and sex hormones has garnered attention in the recent years. MS course improves during pregnancy. In a 2011 meta-analysis of 23 studies that had recruited 13,144 pregnant women with MS, a benefit for pregnant women was apparent, manifested as a decrease in relapse rate (from 0.43 to 0.26 per year during pregnancy); the relapse rate increased to 0.76 in the firstpostpartum year [5]. Notably, the seminal PRIMS study reported that the third trimester was the timeframe in which maximum benefit was illustrated [6]. An observational study corroborated this finding and identified prior administration of disease-modifying treatment as a protective factor against postpartum relapses [7]. The most likely mechanism that mediates the decrease in relapse rate is the action of sex steroids on the immune system, specifically the shift from T_{h1} to T_{h2} response [8]. Recently, a distinct epigenetic profile was described in mononuclear cells of pregnant women with MS, overall indicating a modulated transcription of T-regulatory cells [9].

The aim of the present review was to retrieve and systematically synthesize the available evidence on the effect of menopause and HRT on the course of MS. For a wider appraisal of the effect of sex hormones

* Corresponding author at: Winstanley Rd., SW11 2EU, London, UK.
E-mail address: vaskarageorg@hotmail.com (V. Karageorgiou).

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on MS disease course, relevant evidence on premenopausal women with MS was also sought after.

2. Methods

2.1. Eligibility criteria

Observational studies (cohort, case-control, cross-sectional) recruiting women with MS during premenopausal, menopausal transition or postmenopausal period were deemed eligible. Both prospective and retrospective designs, as well as case series, were acceptable. In addition, interventional studies [randomized-controlled trials (RCT's), non-randomized studies] assessing the effect of estrogen or related modalities in the course of disease in women with MS were included. Animal studies employing the experimental autoimmune encephalomyelitis MS model and *in vitro* studies were excluded.

2.2. Literature search

A comprehensive search was performed in five major databases [PubMed (MEDLINE), Scopus, clinicaltrials.gov, Cochrane Controlled Register of Trials (CENTRAL)] from inception until August 10th, 2019. The search string [("multiple sclerosis" OR MS OR "disseminated sclerosis") AND (menopaus* OR estrogen OR "hormone replacement therapy" OR HRT)] was applied. Wherever applicable, keywords were employed. For a complete assessment of the literature, the first ten pages of Google Scholar were assessed as a proxy of the grey literature. The reference lists of the included studies were screened for potentially relevant articles. No language or date-of-publication restrictions were applied.

2.3. Study selection

The titles and abstracts of all retrieved studies were screened, and articles considered relevant were accessed in full. Any study fulfilling the inclusion criteria was included.

2.4. Outcomes

Pre-specified outcomes in women with MS upon which quantitative evidence was extracted was 1) relapse rate before and after menopause, 2) age at onset of menopause, 3) serum estrogen, estradiol and other sex hormone concentrations, 4) disability before and after menopause, as assessed by scores such as the Expanded Disability Status Scale (EDSS), and 5) the effect of HRT on the quality of life, as documented by disability indices.

2.5. Synthesis

Regarding relapse rates, if the data were provided consistently, a meta-analysis using log incidence rate ratios was pre-planned, assuming Poisson distribution of the relapse counts. The log transformation aids in approximating normality around 0 for this metric [10]. If events were not directly reported, the formulae proposed by Cochrane and a meta-analysis regarding tuberculosis in adults with HIV would be used for indirect extraction of the events and their variance [11,12].

3. Results

3.1. Literature search

The search algorithm yielded 4102 results PubMed: 3,979, clinicaltrials.gov: 6, Scopus: 123. Of these, 161 were deemed potentially eligible and accessed in full. After exclusion of the duplicates, 28 studies were included in the systematic review Fig. 1).

3.2. Patient characteristics

The mean age of included women with MS ranged from 25.4–56.1 years. Twelve observational studies assessed various parameters in menopausal women with MS [13–24]. Diagnosis of menopause was based on clinical history in seven studies [14,16,13,17,18,22,23], and hormonal parameters in two studies [15,20]. In those studies that employed a longitudinal design, this was retrospective with a range of follow-up from 7.2 years to 10.4 years (Table 1).

3.3. Data synthesis

Regarding the relapse rate of MS after menopause, two studies reported on long-term follow-up of women with MS around the onset of menopause [13,17]. The first [13] followed patients for a mean of 3.7 years before and 3.5 years after the onset of menopause and the second [17] for 10 years around menopause. Both studies did not report the relapse rate, nor how relapses were distributed in individuals. However, in the Ladeira et al. study, adjustments were performed regarding disease-modifying treatment (DMT) use. As far as MS stage is concerned, the Baroncini et al. study explicitly reported primary progressive MS (PPMS) as an exclusion criterion, while the Ladeira et al. study included two women with PPMS. In the meta-analysis, relapses per year were similar before and after menopause [risk ratio (RR) 1.21, 95 % confidence interval (CI) 0.91–1.61, $p = 0.218$, I^2 0%) (Fig. 2).

3.4. Serum sex hormone concentrations

Four studies [15,20,25,26] investigated sex hormones in women with MS (n = 577, of whom 133 were post-menopausal). While one study [20] reported an age- and reproductive state-independent decrease of both estrogen and estradiol in women with MS, another study [25] did not find any difference. Two studies [15,26] reported decreased anti-Müllerian hormone (AMH) concentrations in women with MS compared with healthy controls. Given the discrepant mean age of women in these studies [39.3 (11.67) vs. 25.4 (4.9) years for estrogen concentrations], pooling of the results was not performed, as it was anticipated that natural aging would confound the result. No evidence was available regarding the potential differences of age-matched women with differing MS phenotypes.

3.5. Sexual function

In a recent study [23], the prevalence of sexual dysfunction, in the domains of arousal, in a two-hospital cohort was 64.5 %. Gava et al. [22] underlined the link of sexual dysfunction in women with depressive symptomatology, as this was manifested by the Beck's Depression Inventory (BDI) scale. In their study population, 56 women were experiencing menopause. Lombardi et al. [27] estimated that there is a trend for an association between17β-estradiol concentrations and sexual desire in women with MS.

3.6. Intervention studies

Two RCTs [28,29] and a secondary analysis of one of these [30] were included. Only one study [29] was described as being double-blinded. This study estimated a decrease in the annualized relapse rate in women to whom low-dose estriol was administered.

4. Discussion

Through systematically searching the literature, a profile of a modest association of sex steroids with MS course can be sketched. Observational evidence, mostly from studies recruiting premenopausal women, suggests that serum estradiol concentrations in women with MS may be different [15,20,26,44,15], although clinical heterogeneity

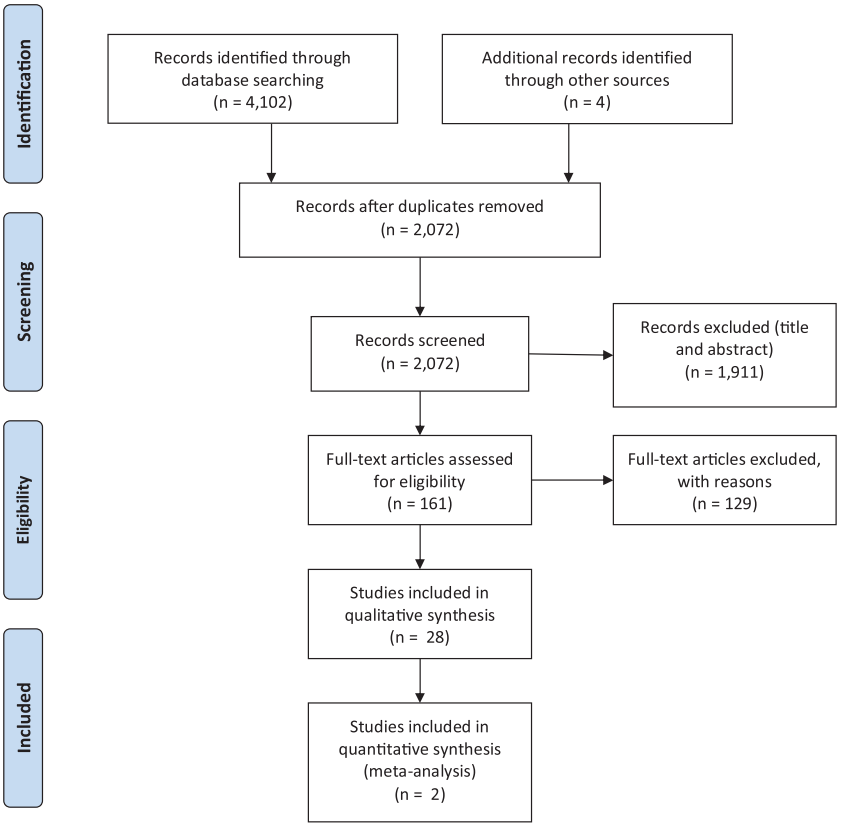

Fig. 1. PRISMA flowchart.

of these studies precludes a meaningful synthesis of the data; on the contrary, studies reporting null differences have also been conducted [25]. Longitudinal studies assessing the influence of sex steroids in a single-generation cohort, ideally from menarche to post-menopause, are lacking.

As MS has become a controlled, yet progressive, lifelong disease, it is anticipated that more women will be reaching menopause and be facing its consequences. Concerns for earlier onset of (iatrogenic) menopause have been raised. A 2018 case-control study recruiting 86 women with MS reported an inverse correlation of IFN-1β and methylprednisolone treatment with menopause onset [19]. Furthermore, postmenopausal osteoporosis in women with MS may be aggravated by prolonged inactivity [31]. Combined with the cumulative effect of corticosteroids on bone, administered mainly for the flares of MS, the risk for osteoporosis in MS women is high. A 2015 meta-analysis summarizing the results from 9 large cohort studies estimated a relative risk of 1.58 for fractures in subjects (predominantly women) with MS [32]. From the available evidence, it appears that the age at menopause onset is not different in women with and without MS [33].

The present analysis does not support a change in the relapse rate after menopause. However, essential presupposition in both included studies [13,17] is the proportionality of the effect of menopause across the peri-menopausal period. Menopausal transition may coincide with advance to progressive forms, as evidenced in a cohort study where the mean age of the onset of progression was 45.5 (10.0) years [34]. Hence, it may be hypothesized that other patterns of MS stage / menopause interactions are at play. For instance, women with less disability could benefit more from a later onset of menopause (i.e. a sustained action of estrogens). However, investigation of these issues is beyond the scope of this review.

Given the neuroprotective effects of estrogens [35], counteracting the loss of this protection with hormone replacement therapy (HRT) seems appealing. Animal studies have underlined a beneficial effect of estrogen receptor-β (ERβ) signaling in promoting remyelination [36]. However, clinical evidence does not offer clear messages. In a small (n = 19) questionnaire-based study in post-menopausal women, no patient under HRT reported a worsening of symptoms [18]. On the other hand, Holmqvist et al. reported worsening of MS symptoms after menopause in patients on HRT compared to patients not on HRT. The two interventional studies by Pozzili [28] and Voskuhl [29] reported a decrease in enhancing lesions and in relapse rate, as well as improvement in cognitive performance, without any unanticipated alarming event. Still, follow-up time was not sufficient, nor were the studies powered to detect the cardiovascular events [37]. It should be noted, however, that, in the study of Voskuhl et al. [29], 26 women treated with estriol experienced light vaginal bleeding (“spotting”). Nevertheless, HRT schemes commonly used in postmenopausal women, such as oral or transdermal 17-beta estradiol have not been studied.

A domain where HRT has not been directly tested for its efficacy in women with MS is sexual dysfunction, a condition commonly underdiagnosed in women with MS [38], Sexual dysfunction can be precipitated both by the disease itself and menopause. The prevalence of the condition ranges between 42–64 % of patients with MS. In one study sexual dysfunction was marginally associated with serum concentrations of 17-beta estradiol (Lombardi). Studies comparing rates of sexual dysfunction between women with MS before and after estrogen treatment are not available. Vaginal dryness, and dyspareunia can be effectively treated with vaginal estrogen modalities [39].

In conclusion, the progress of MS often accompanies the transition to menopause, however, a causative effect of menopause on disease progression cannot be established. There are circumstantial reports of a beneficial effect of estrogens on disease progression. Evidence on a frank decrease of relapse rate, as it has been suggested, is not replicated on an aggregate level. As disability naturally follows aging, future studies should aim at following women longitudinally and treat menopause as a landmark event.

Table 1
Patient characteristics in the studies included in the qualitative analysis.

id	First author, year	Women with MS	Age (years)	Menopausal women (n)	Women on HRT or OC (n)	Comparison	Outcomes of interest	QA
Observational studies								
1. Disability								
1	Smith, 1992	19	56.1	19	8 (HRT)	Postmenopausal MS on HRT vs. postmenopausal MS	Improvement of symptoms on HRT (reported)	High
2	Holmqvist, 2006	128	51 (24, 71)[+]	72	35 (ever-users)	Postmenopausal MS on HRT vs. postmenopausal MS	Worsening of symptoms on HRT (reported)	High
3	Bove, 2015b	724	57.4 (7.7)	364 (any cause)	59	EDSS before and after menopause	↑ disability after menopause	Low
4	Ladeira, 2018	37	45.2 (4.0)	37	5 (ever-users)	Relapse rate before and after menopause	↓ relapse rate after menopause	Low
5	Baroncini, 2019	148	NA	148	5	Relapse rate before and after menopause	↓ relapse rate after menopause	Low
2. Hormonal concentrations								
6	Zakrzewska-Pniewska, 2011	46	39.3 (11.7)	19	NA	MS vs. age-, menopausal status-matched controls	↓ estradiol, ↑ progesterone	High
7	Graves, 2018	415	42 (23, 63)[+]	114 (undetectable AMH)	110 (including OC)	MS vs. controls	↓ AMH. AMH was associated with disability status, *marginally* with grey matter (negatively), irrespectively of HRT use	Low
8	Trenova, 2013	35	34.8 (9.0)	0	NA	RRMS (case series)	↓ estrogen, progesterone in 60 %	High
9	Thone, 2014	76	29.1 (4.4)	0	38 (OC)	RRMS vs. controls	↓ AMH AMH undetectable in women on OC	Low
10	Talaat, 2018	40	25.4 (4.9)	0	0 (excluded)	RRMS vs. age-matched controls	↔ estrogens	Unclear
11	Kempe, 2018	25	OC: 36 (25, 39) No OC: 27 (22, 40)	0	12 (on OC)	MS vs. controls, both of reproductive age	↑ immune activation mediator (as proxied by CTLA-4) not associated with estrogen production	High
3. Sexual function								
12	Lombardi, 2011	54	36.7 (27, 44)	NA	8 (on OC) (excluded)	MS not on OC	Sexual dysfunction in 57 % Associated with 17β-estradiol	Unclear
13	Gava, 2019	153	47.3 (10.5)	56	0	MS not on OC	Sexual dysfunction in 42 % Associated with higher depression scores (BDI)	Low
14	Konstantinidis, 2019	248	45.8 (8.5)	96	NA	MS	Sexual dysfunction in 64.5 %	Low
4. Age at menopause								
15	Boru, 2018	86	45.3 (4.8)	86	NA	Postmenopausal MS vs. postmenopausal controls	No difference	Low
5. Other outcomes								
16	Bove, 2017	217	49.4 (14.3)	106	29	MS + neuromyelitis optica stratified by age of onset	Hormonal exposures and age at disease onset No difference in women on HRT.	Unclear
17	Langer-Gould, 2017	397	36.6 (12.2)	70	287 (on OC)	Newly diagnosed MS/ CIS, stratified by OC use vs. healthy controls	No trend for length of OC use associated with MS/ CIS	Low
18	Bove, 2016	95	56.6 (3.8)	95	61	Postmenopausal women with MS	HRT associated with improved physical functioning	Low
19	Holmqvist, 2009	23	41 (26, 51)	0	7 (on OC)	MS using OC	OC use phase associated with more intense symptomatology	High (response rate)
20	Kempe, 2015	17	34 (24, 44)	0 (pre-menopausal)	All (on OC)	MS (case series)	↓ MS activity (vertigo, weakness, urinary symptoms, stiffness)	High
21	Sioka, 2015	46	33.7 (8.2)	0	0	Premenopausal women with MS	Age at menarche associated with bone mineral density	High
22	Perlman, 2016	1	NA	NA	NA	Case report	IFN-1β associated with increased estrogen and bleeding in 1 post-menopausal woman	NA
23	Rojas, 2016	49	NA	NA	0 (excluded)	MS before, MS after menopause vs. age-matched males	In "before" group: ↑ cortical, total brain and brainstem volumes	High
24	Bove, 2018	162	Current HRT: 31.4 (7.2) Previous HRT: 40.3 (7.8) Never HRT:	NA	46 (current users) 66 (past users)	MS/ CIS *and* OC use *and* DMT. Stratified by OC use: 1 Never 2 Past Current	No trend for differential effect on risk of relapses $RR_{3\ vs.\ 1} = 0.89$	Low

(*continued on next page*)

Table 1 (*continued*)

id	First author, year	Women with MS	Age (years)	Menopausal women (n)	Women on HRT or OC (n)	Comparison	Outcomes of interest	QA
			37.9 (10.6)					
25	Jacob, 2017	160	31.5 (26, 39)*	NA	1 (excluded)	1 Predominantly premenopausal women with RRMS	Estradiol associated with MS risk	High (reporting)
Interventional studies								
26	Pozzili, 2015	149	EE 20 μg: 28.9	0	50 (EE 20 μg + DSG 150 μg)	EE 20 μg vs. EE 40 μg	↓ enhancing lesions in EE 20 μg group	JADAD 1,1,0,0,1 **
27	De Giglio, 2016 (secondary analysis of 17)	149	(6.8) EE 40 μg: 29.9 (5.6)		49 (EE 40 μg + DSG 125 μg)	EE 20 μg vs. EE 40 μg	↑ cognitive performance in IFN-β + HRT group	JADAD 1,1,0,0,1 **
28	Voskuhl, 2016	164	Estriol: 37.7 (7.6) Placebo: 37.1 (7.3)	NA	83 (on estriol and progestin)	Estriol vs. placebo	↓ relapse rate in estriol group Trend for cortical grey matter atrophy deceleration	JADAD 1,1,1,1,1

Data are given as mean (SD). +: median and range; *: median and interquartile range (IQR); **: not double blinded. ↓: decrease; ↑: increase; 1: no difference. For observational studies, the RoB 2 score is reported. For intervention studies, the JADAD score is reported.
AMH: anti-Müllerian hormone; CIS: clinically isolated syndrome; DSG: desogestrel; EDSS: Expanded Disability Status Scale; EE: ethinyl-estradiol; HRT: Hormone replacement therapy; JADAD: Jadad scoring system; IFN: interferon; MS: multiple sclerosis; NA: not available; OC: oral contraceptives; QA: Quality assessment (High, Low, Unclear: high, low and unclear risk of bias respectively); RCT: randomized controlled trial; RRMS: relapsing-remitting multiple sclerosis; SD: standard deviation.

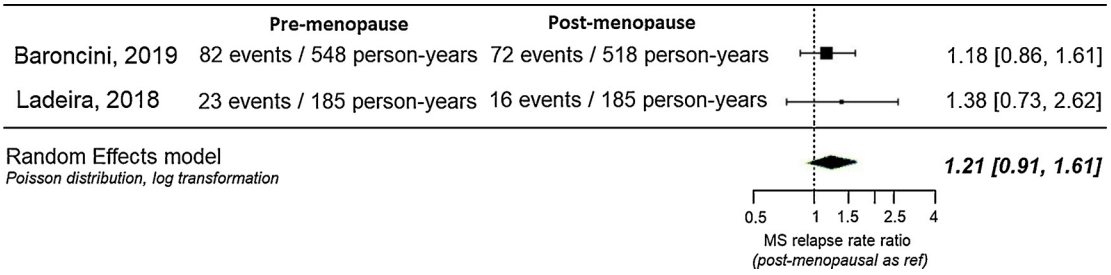

Fig. 2. Forest Plot for the pooled effect estimate for relapse rate before and after menopause.

Contributors

Vasilios Karageorgiou performed the literature search, synthesized the evidence and wrote the draft of the manuscript.

Irene Lambrinoudaki conceived the objectives, conducted the analysis of the results and undertook critical revision of the manuscript.

Dimitrios G. Goulis conceived the objectives, conducted the analysis of the results and undertook critical revision of the manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

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Provenance and peer review

Peer review was directed by Professor Martina Doren independently of Irene Lambrinoudaki, one of the authors and co-Editor in Chief of *Maturitas*, who was blinded to the process.

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