The impact of menopause on multiple sclerosis: a multicentre, retrospective, observational study

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Background and objectives

- Menopause (MP) is a physiological event in a woman's life that marks the end of reproductive competence due to the permanent cessation of ovarian follicular activity, and it is linked to a fall of estrogens blood levels[1];
- MP is defined retrospectively by the final menstrual period (FMP), beyond which no menses occur for 12 months[2];
- In animal model of multiple sclerosis (MS) estrogens have been associated with both inflammation and neuroprotection[3,4];
- Few studies have addressed the role of MP in MS: some have shown a worsen of subjective symptoms after MP[5,6], one found a higher disability accumulation after MP[7];
- Our aim was to define the clinical impact of natural MP on MS course;

Methods

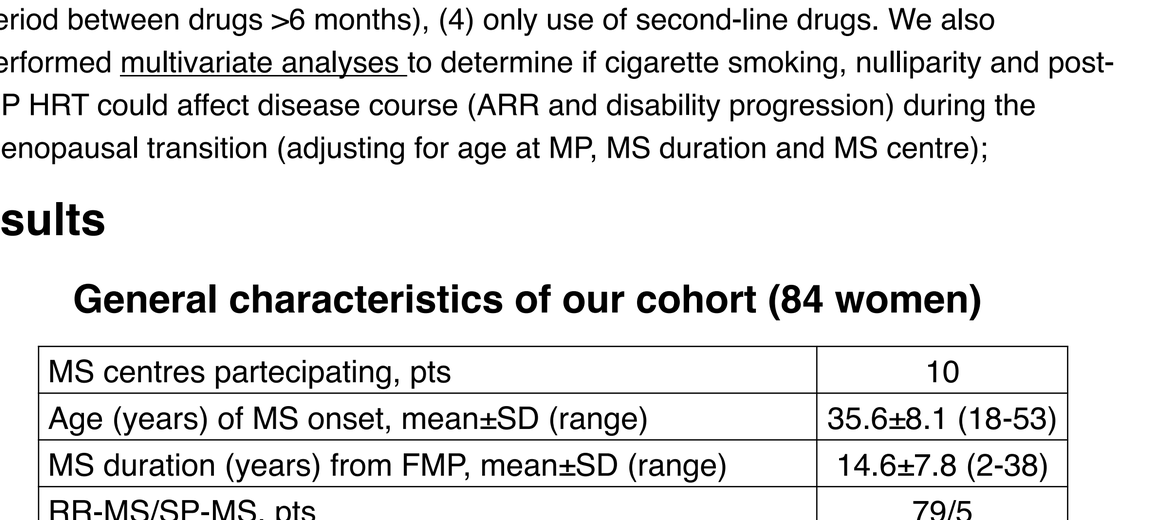
- **Study design:** observational, retrospective, multicentre;
- **Inclusion and exclusion criteria:** we included women with MS and a natural MP onset after 2005. We excluded patients (pts) with: MS onset <3 years pre-FMP, primary progressive MS, uncertain date of FMP, previous use of cyclophosphamide/ mitoxantrone, hysterectomy/endometrial ablation, neoplasm/HIV, use of hormonal replacement therapy (HRT) <3 years pre-FMP;
- **Data collection:** over an observational period set to 2-4 years pre and post-FMP we recorded ARR, annual EDSS score, disease modifying therapies (DMTs) received, demographics, pregnancies, cigarette smoking, artificial inseminations (AIs), HRT and comorbidities;
- **Statistical analyses:** primary endpoint was to compare ARR and EDSS score variation (reference: EDSS at FMP) before and after MP. Given the possibility that some non-controllable variables could affect the measured outcomes we performed different sensitivity analyses (SAs) excluding patients with: (1) secondary progressive (SP) MS, (2) AIs and/or natalizumab (NAT)/fingolimod (FTY) suspension, (3) discontinuous therapy (i.e. starting DMTs after >6 months from the beginning of the observational period, suspension of DMTs >6 months before the end of observational period, interval period between drugs >6 months), (4) only use of second-line drugs. We also performed multivariate analyses to determine if cigarette smoking, nulliparity and post-MP HRT could affect disease course (ARR and disability progression) during the menopausal transition (adjusting for age at MP, MS duration and MS centre);

Results

General characteristics of our cohort (84 women)

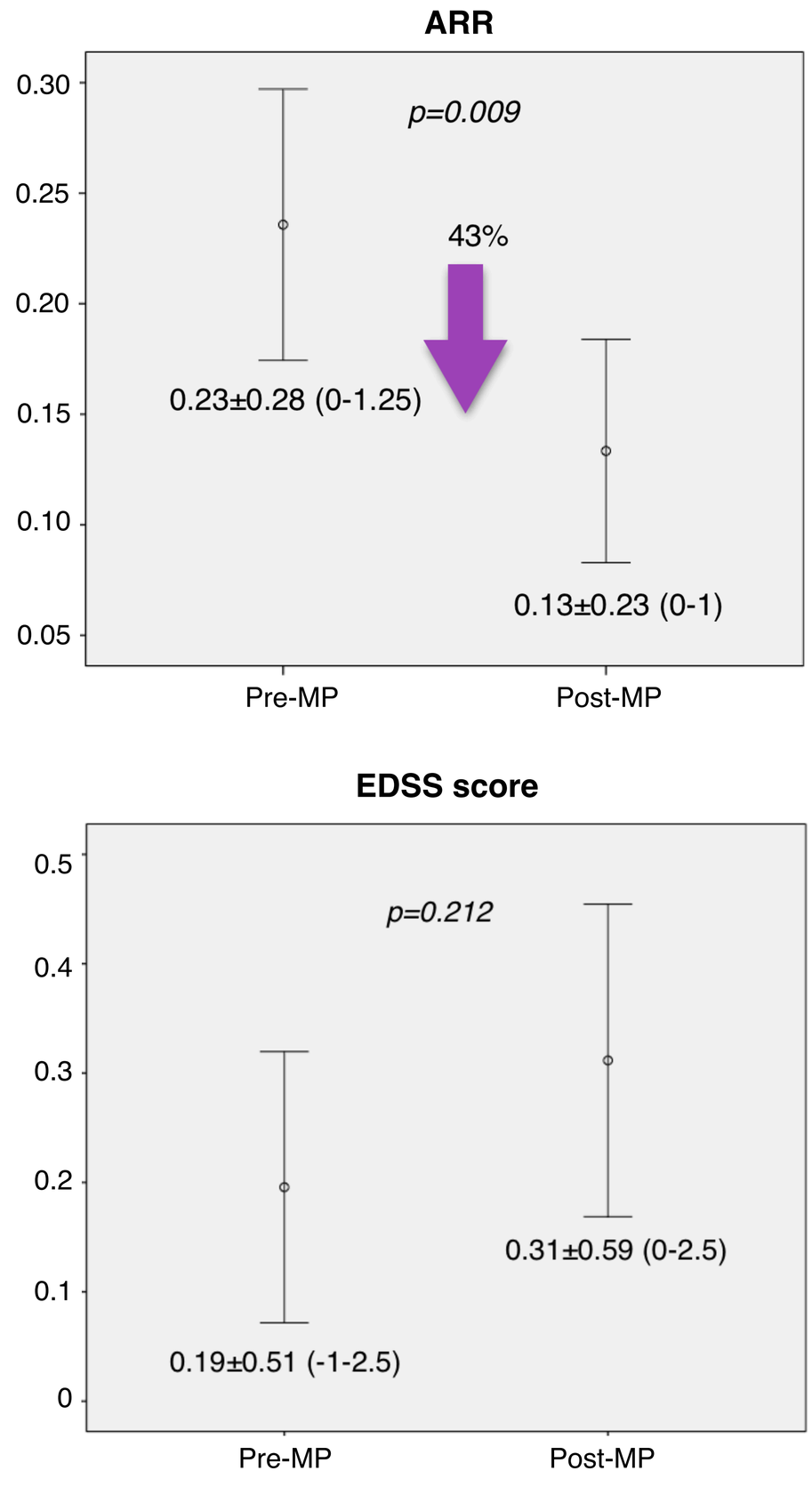
MS centres partecipating, pts	10
Age (years) of MS onset, mean±SD (range)	35.6±8.1 (18-53)
MS duration (years) from FMP, mean±SD (range)	14.6±7.8 (2-38)
RR-MS/SP-MS, pts	79/5
Age (years) at FMP, mean±SD (range)	50.2±3.2 (43-57)
Nulliparous, pts	21(25%)
Artificial inseminations, pts	0
HRT post-FMP, pts	4 (5%)
Cigarettes smokers, pts	27 (32%)
Observational period pre/post-FMP (years), mean±SD	3.7±0.6/3.5±0.7

Treatment history



During the observational period the majority of patients (93%) receive DMTs, mainly first-line agents (glatiramer acetate, interferon-beta, teriflunomide, dimethyl fumarate). Few patients (2%) received only drugs approved as second-line (FTY, NAT, alemtuzumab), while 18% received both first and second-line therapies. Five (6%) patients suspended NAT/FTY during observational period.

Clinical course of MS during menopausal transition



The ARR showed a significant reduction after MP onset. This finding remained significant in all sensitive analyses ($p<0.05$).
The disability progression rate showed an increase trend after MP, without reaching statistical significance in the pivotal analysis. It resulted significant ($p=0.038$) only after exclusion of women with a discontinuous treatment (sensitive analyses 3).
The multivariate analyses did not find any statistically significant effect ($p>0.1$) of cigarette smoking, nulliparity and HRT on disease course during menopause transition.

Conclusions

- Limits of our study are mainly small sample size, lack of MRI data and retrospective design. However, it is the first time that a clinical outcome such as ARR is measured during menopausal transition in MS patients;
- The ARR showed a significant and consistent reduction after MP;
- The disability progression rate showed an upward trend after MP, but it resulted statistically significant only after exclusion of women with a discontinuous treatment. This could be due to a "masking effect" linked to treatment fluctuations in this group. This finding would be in agreement with a previous study were it was reported a faster disability worsening after MP[7];

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