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 levels1;
- MP is defined retrospectively by the final menstrual period (FMP), beyond which no menses occur for 12 months2;
- In animal model of multiple sclerosis (MS) estrogens have been associated with both inflammation and neuroprotection3,4;
- Few studies have addressed the role of MP in MS: some have shown a worsen of subjective symptoms after MP5,6, and better disability at menopause6,7;
- 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 with: (1) MS onset ≥ 3 years pre-FMP, (2) MP age ≥ 53 years, (3) pregnancy during the menstrual cycle, (4) only use of second-line drugs. We also included patients with: (2) AIs and/or natalizumab (NAT)/natalizumab (NT); (2) suspension of DMTs >6 months before the end of observational period, interval between drugs >6 months (SAs);
- Data collection: over an observational period set to 2-4 years pre and post-FMP we recorded AR, 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)/natalizumab (NT) 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)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Pre-MP</th>
<th>Post-MP</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>46.9±7.8 (30-54)</td>
<td>51.2±8.3 (36-55)</td>
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<tr>
<td>MS duration (years)</td>
<td>13.6±7.3 (6-26)</td>
<td>17.2±8.3 (8-30)</td>
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<tr>
<td>RR/MS/SP/MS, pts</td>
<td>42/23/28/5</td>
<td>41/24/26/5</td>
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<tr>
<td>Nulliparous, pts</td>
<td>21 (25%)</td>
<td>26 (25%)</td>
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<tr>
<td>Artificial inseminations, pts</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>HRT post-FMP, pts</td>
<td>3 (4%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Cigarettes smokers, pts</td>
<td>25 (32%)</td>
<td>27 (33%)</td>
</tr>
<tr>
<td>Observational period pre/post-FMP, yrs</td>
<td>3.7±0.6±3.5±0.7</td>
<td>4.1±0.7±3.8±0.9</td>
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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<0.008) only after exclusion of women with a discontinuous treatment (sensitive analyses 3).

The multivariate analyses did not find any statistically significant effect (p>0.01) 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 MP7;

References