Multiple Sclerosis and Related Disorders 20 (2018) 164–168

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Uncovering the link between reproductive factors and multiple sclerosis: A case-control study on Iranian females

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ARTICLE INFO

Keywords:
Multiple sclerosis
Females
Reproductive
Pregnancy

ABSTRACT

Background: Increase of MS prevalence in females compared to males, especially in reproductive age, highlights the important role of reproductive factors in MS pathology.
Objectives: We examined the association between females' reproductive age-related factors and MS risk.
Methods: A case-control study including 399 cases and 541 controls was carried out. The adjusted associations between MS risk and reproductive variables including age at menarche, oral contraceptive pills (OCPs) use history, OCP usage duration and age at first use, history of assisted reproductive technologies (ARTs) use, parity history, age at first childbirth and the number of parities, abortion and exclusive breast feeding > 2 months were assessed.
Results: We found protective relationships between MS and older age at menarche (OR = 0.90 {95% CI = 0.82–0.98}), ART use history (OR = 0.45 {95% CI = 0.21–0.99}), older maternal age at first childbirth (OR = 0.94{95% CI = 0.89 − 0.99}) and higher number of parities(OR = 0.61 {95% CI = 0.49 − 0.75), whereas using OCPs was associated with higher risk of developing MS (OR = 1.80 {95% CI = 1.35–2.41}).
Conclusions: Links were noted between a number of reproductive factors and risk of MS.

1. Introduction

Multiple sclerosis (MS) is a common progressive disease of central nervous system (CNS) with unknown etiology that is considered as one of the main cause of disability in young adults (Sadovnick and Ebers, 1993; Milo and Kahana, 2010). MS sex ratio is often reported to be 3:1 which is increasing over the last decades worldwide (Alonso and Hernán, 2008; Orton et al., 2006). Iranian national data has also been indicated a sharp increase in female MS prevalence (more than 50%) during 2002–2008 (Etemadifar et al., 2013; Sahraian et al., 2010). A focus on sex ratio in MS, may provide key insights into the etiology and pathology of disorder in addition to health care strategies and research areas (Sellner et al., 2011). The female preponderance in MS incidence reflects a plausible greater susceptibility to environmental changes. Indeed changes in eating habits, obesity, smoking, early menstruation, using contraceptive pills, hormonal replacement therapies, enhanced pregnancy age, type of occupations and urbanity, are all just a few examples of life style changes over the last decades which might affect the risk of MS in females (Hedström et al., 2015).

In addition to environmental changes, there is substantial evidence suggesting reproductive factors as an issue which may explain increased MS prevalence in reproductive-aged women (Magyari et al., 2013). For example the role of puberty in development of MS was reviewed by Chitnis. Result indicated that puberty is associated with MS risk particularly in females; as such post-pubertal reproductive period was considered as a critical period for development of disorder (Chitnis, 2013). Ramagopalan et al. suggested that earlier age at menarche increases the risk of MS in females, however further studies are needed to uncover whether this earlier age directly involved in MS etiology or not (Ramagopalan et al., 2009). Despite a large body of researches, the association between oral contraceptive pills (OCPs) and MS is still a matter of controversy. Surprisingly, a few studies have indicated that use of OCPs could be associated with both a decreased or increased risk of MS incidence or onset of symptoms, while others have shown no link.

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https://doi.org/10.1016/j.msard.2018.01.019
Received 26 August 2017; Received in revised form 6 January 2018; Accepted 21 January 2018

For instance, Alonso et al. showed that MS incidence was 40% lower in OCP users. They claimed that hormonal changes due to OCP use may be associated with a short-term reduction in MS risk (Alonso et al., 2005). Similarly, Holmqvist et al. found that use of OCPs can be correlated with a delay in the onset of disease (Holmqvist et al., 2010). On the other hand D'hooghe et al. indicated that in progressive onset MS, a more rapid progression of disabilities occurred when women reported the use of OCPs (D'hooghe et al., 2012). However finally a few researchers did suggest no significant association between OCP use and MS (Villard-Mackintosh and Vessey, 1993; Thorogood and Hannaford, 1998). Alonso and Clark reviewing the published papers reported that existing evidence does not support a significant effect of OCP use on the risk of MS or OCP may just delay the onset of MS symptoms (Alonso and Clark, 2009). Given above it seemed that the question on OCP and MS need to further evaluation; for example to be answered in new populations.

To significance of this study, other controversial risk factors such as pregnancy and number of parity and their effects on MS have been reassessed. Results of Ponsonby et al. have considered pregnancy as a protective factor for developing MS (Ponsonby et al., 2012). Furthermore in a cohort study on 1403 MS patients of both sex, Magyari et al. demonstrated that childbirths within 5-years before onset of clinical symptoms may reduce the risk of MS in females (Magyari et al., 2013). However, on the other hand, Leibowitz et al. claimed that pregnancy may increase the risk of MS (Leibowitz et al., 1967) and interestingly, some other studies have suggested no association between parity history and MS (Thorogood and Hannaford, 1998; Hernan et al., 2000). Furthermore, more recently other factors such as the number of parity or breastfeeding are suggested to have a reverse effect on MS risk or be protective against MS clinical activity and relapses (Langer-Gould et al., 2009; Pakpoor et al., 2012).

Understanding the role of reproductive factors in MS pathophysiology may help identification of at-risk population and development of preventive strategies. Given to the controversy existed in the literature, there was an emergency need to clarify link of reproductive factors and chance of developing MS in new samples. Furthermore, there is little information regarding cumulative effect of all reproductive factors on developing MS; thus to fill the gap, we conducted a population-based case-control study aimed at examining the association of reproductive age-related factors with MS in a large sample of females living in Tehran, Iran.

2. Materials and methods

2.1. Selection of cases and controls

We enrolled a total of 940 females aged 15–50 years, including 399 cases with confirmed MS diagnosis based on the 2010 McDonald criteria as well as positive MRI who had registered at Iranian Multiple Sclerosis Society between August 2013 and February 2015 and were resident within 22 districts of Tehran, and 541 females with no MS diagnosis as controls. Standard Random Digit Dialing (RDD) method was used for random selection of controls from the same source population of cases and proportional to population size of each 22 districts of Tehran. The response rates among case and control groups were 96% and 70%, respectively.

2.2. Measurements

All participants were interviewed based on a standardized questionnaire including information regarding demographic (i.e. age, education, marital status and ethnicity) and reproductive factors (i.e. age at menarche, OCPs use history, usage duration and age at first use, parity history and age at first childbirth, abortion, assisted reproductive technology (ART) use and exclusive breast feeding > 2 months history).

Study interviewers were selected based on their communication ability and well-doing the standardized interview. For standardizing the data collection procedure, we systematically trained the 10 interviewers. All of selected interviewers had to follow the same detailed protocol of interview. For this, we provided a voice file containing the standard approach of asking each question. The interviewer had to ask the study items as the same as voice file. We strongly tried to avoid interviewers from any unnecessary clarifying of questions in cases and also any skip from the study protocol or the rules of questionnaires. Also, we strictly monitored the data collection activities for detecting any interviewer bias by randomly recording interviews. At the start of each interview, the main study objectives were fully elucidated for both of study groups. Moreover, the clinical signs and characteristics of MS in the start of study were fully elucidated for general population. Finally, the following information was equally extracted in both study groups: demographic factors i.e. age, educational status, marital status. We acquired the approval of the ethics committee of Tehran University of Medical Sciences regarding the method of data gathering.

2.3. Statistical analysis

Quantitative and qualitative data were described as mean (standard deviation) and frequency (percentage). We used the independent *t*-test to analyze the association between each of continuous independent variables (i.e. age, age at menarche, age at first childbirth, age at first OCPs use) with MS; and the chi-square test for categorical variables (i.e. marital status, education, parent ethnicity, history and duration of OCPs use, history and number of parities, abortion history, exclusive breastfeeding > 2 months and ART use history). Simple (univariate) logistic regression model with MS as the response variable was used to estimate the unadjusted odds ratios with 95% confidence intervals (95% CIs) between the reproductive variables and MS. Furthermore, we assessed the independent effects of the reproductive variables after adjusting for potential confounding variables including age, marital status, education and ethnicity, using multiple logistic regression model and backward selection method (Mansournia et al., 2017a). We summarized the results in terms of adjusted ORs (95% CIs). To avoid unnecessary and inefficient sub analyses, age at first birth for nulliparous women and age at first OCP use for persons without any history of OCP use were imputed by the mean age at first birth for parous women and the mean age at first OCP use for OCP users, respectively (Thompson, 1993). To avoid sparse-data bias, we combine adjacent sparse categories for categorical variables such as education (Greenland et al., 2016). All statistical analyses were performed using SPSS version 20 and Stata version 12.

3. Results

The mean (SD) age of cases and controls were 30.6 (7.6) and 31.7 (9.0), respectively. The history of OCPs intake in cases was significantly higher than controls (P = 0.01). However the mean age at first use of OCPs, history of parity, exclusive breast feeding and using ART were all significantly lower among MS group. However, there were no significant differences in abortion history, duration of OCP use and age at first childbirth between study groups (Table 1).

3.1. Univariate analysis

As shown in Table 2, univariate logistic regression analysis demonstrated that risk of developing MS is affected by marital status, education, age at menarche, OCPs use, age at first usage of OCPs, ART history, parity history, number of childbirths and exclusive breastfeeding more than 2 months. Indeed results showed that each one-year increase in age at menarche, reduced the risk of developing MS by 8% (OR = 0.92 {95% CI = 0.84–0.99}); using OCPs was associated with a 1.4 times increase in MS risk (OR = 1.40 {95% CI = 1.08–1.82}) but this risk decreased by 5% per 1-year increase in age at first use (OR =