



# Is Fertility Affected in Women of Childbearing Age with Multiple Sclerosis or Neuromyelitis Optica Spectrum Disorder?

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## Abstract

Multiple sclerosis (MS) is a chronic immune-mediated demyelinating disease of the central nervous system (CNS), which is more prevalent among women of childbearing age. Neuromyelitis optica spectrum disorder (NMOSD) is a severe autoimmune disease of the CNS with similar prevalence features to MS and has recently been considered a different entity from MS. Measuring ovarian reserve is one way of evaluating fertility. Anti-Müllerian hormone (AMH) is a peptide hormone produced by ovarian granulosa cells of early follicles and is considered to be a marker for ovarian reserve. With MS and NMOSD predominance in young women, the present study aimed to address the possibility of these diseases affecting fertility by measuring AMH levels in MS and NMOSD patients and comparing it with healthy controls. The present study included 23 relapsing-remitting MS (RRMS) patients, 23 seronegative NMOSD patients, and 23 healthy age-matched controls between 18 and 45 years of age. Serum samples of the three groups were collected, and the AMH levels were measured with AMH Gen II Enzyme-Linked Immunosorbent Assay, Beckman Coulter kit. In the present study, the AMH levels did not differ significantly between the groups ( $p = 0.996$ ). The mean AMH in the RRMS group was  $3.59 \pm 0.55$  ng/ml compared with the mean of  $3.60 \pm 0.50$  ng/ml in healthy controls. The mean AMH levels in the NMOSD group were  $3.66 \pm 0.61$  ng/ml. Lower levels of AMH were found to be negatively associated with annualized relapse rate (in both groups of patients) and MS severity score. However, the difference was not significant. In NMOSD patients, the serum levels of AMH were negatively associated with disease duration ( $r = -0.42$ ,  $p = 0.023$ ). There had been a significant negative correlation between mean AMH serum levels with Expanded Disability Status Scale (EDSS) at the time of diagnosis and at the time of study in the NMOSD group ( $r = -0.402$ ,  $p = 0.03$  and  $r = -0.457$ ,  $p = 0.014$ , respectively). There was not a significant difference in mean serum AMH levels between RRMS and NMOSD patients compared with that of healthy controls. Further studies with larger sample sizes should be conducted, which take more variables affecting fertility in women with either RRMS or NMOSD into account to put an end to the controversial issue of fertility in this area.

**Keywords** Multiple sclerosis · Neuromyelitis optica spectrum disorder · Devic's disease · Anti-Müllerian hormone · Fertility · Pregnancy

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## Introduction

Multiple sclerosis (MS) is a chronic immune-mediated demyelinating disease of the central nervous system (CNS) and the second most common cause of neurological disability in young adults after trauma (Calabresi 2004; Goldenberg 2012; Koch-Henriksen and Sørensen 2010). It is more prevalent among the youth with an onset age of 20–40 and a female to male ratio of 3:1 (Greer and McCombe 2011; Niedziela et al. 2014). It affects the white and gray matter of the brain as well as the spinal cord and optic nerve, thus causing a wide variety of neurological and cognitive symptoms. Clinically, the patients may present with the visual, motor, sensory, or cognitive disturbances or dysfunction of the bowel and/or

bladder (Joy and Johnston 2001; Love 2006; Swingler and Compston 1992).

With MS affecting predominantly women of childbearing age, the effect of the disease on pregnancy has been investigated in many studies (Abramsky 1994; Dahl et al. 2005; Ferrero et al. 2004; MacDonald et al. 2018; Weber-Schoendorfer and Schaefer 2009). However, it is not yet fully known whether MS affects fertility in female patients (Cavalla et al. 2006; Dwosh et al. 2003; Hedström et al. 2014). Women with MS seem to have fewer children and seek more fertility treatments for which multiple contributing etiologies have been suggested (Hellwig and Correale 2013; Jalkanen et al. 2010). There is evidence showing a decrease in fertility as a result of MS medications (Amato and Portaccio 2015; Cavalla et al. 2006). On the other hand, it has been suggested that MS patients tend to avoid pregnancy by choice (Borisow et al. 2012; Thöne et al. 2015). According to research, decreased fertility may also be due to the disease itself (Thöne et al. 2015).

Previously considered a subtype of MS, neuromyelitis optica spectrum disorder (NMOSD) is a severe autoimmune disease of the CNS, particularly affecting the optic nerve and the spinal cord (Kessler et al. 2016; Pandit 2015). Classic hallmarks of the disease are acute attacks of optic neuritis (ON) and longitudinally extensive transverse myelitis (LETM), leading to visual, motor, sensory or cognitive disturbances with a possibility of causing urinary and bowel dysfunctions (Kessler et al. 2016; Kleiter and Gold 2016; Zarei et al. 2018). Endocrinopathies have also been reported in patients with lesions to diencephalon in the brain (Pittock and Lucchinetti 2016).

Diagnosis and pathophysiology of the disease are linked to the presence of highly sensitive and specific anti-aquaporin-4-antibodies (AQP4-abs) found in the serum of the majority of patients. NMOSD is more prevalent among women, and the female to male ratio is as high as 9:1 in some AQP-4-antibody positive patients (Kim et al. 2011; Verkman et al. 2013).

Predominantly affecting women of childbearing age (Ajmera et al. 2018; Borisow et al. 2017), there have been researches evaluating the effect of pregnancy on the course of NMOSD. However, the data on the effect of the disease on the reproductive system and fertility is scarce (Borisow et al. 2018).

Measuring ovarian reserve is one way of evaluating fertility. Anti-Müllerian hormone (AMH) is a peptide hormone produced by ovarian granulosa cells of early follicles and is considered to be a marker for ovarian reserve, describing the quality and content of the ovarian follicles at a given time. Serum levels of AMH rise during childhood peaking at puberty and remain fairly constant through adulthood, gradually decreasing to below detection limit by menopause. The serum concentration of AMH is gonadotropin-independent and unrelated to the menstrual cycle (Anderson et al. 2012; Kelsey et al. 2011; Lee et al. 2012; Visser et al. 2012).

AMH levels have been reported to be lower in women of reproductive age affected by MS, thus proposing an independent role for the disease in fertility. The same finding has been reported in NMOSD (Thöne et al. 2015; Thöne et al. 2018).

The present study aimed to measure serum levels of AMH in non-pregnant women of reproductive age with relapsing-remitting MS (RRMS) and NMOSD and compare them with serum levels in non-pregnant healthy controls.

## Materials and Methods

### Study Population

The present study included women of reproductive age attending the outpatient clinic for their routine checkups from September 2018 to December 2018 and age-matched healthy women of reproductive age from hospital staff as a control group.

For the MS group, 23 women, diagnosed with RRMS, and fulfilling revised McDonald's criteria in 2018 (Thompson et al. 2018), who were willing to participate in the study, were included. Patients in this group were under treatment with disease-modifying drugs at the time of the study, and since they were diagnosed with MS.

Twenty-three women diagnosed with NMOSD were also recruited. All of the patients were negative for AQP4-Ig, and their diagnosis of NMOSD was made according to the most widely accepted diagnostic criteria (Wingerchuk et al. 2015). All of the patients were willing to participate in the study and were under treatment with the monoclonal antibodies at the time of the study, and since they were diagnosed with NMOSD.

The control group consisted of 23 healthy female hospital staff of reproductive age who were willing to participate and were taking no medication at the time of study.

In the present study, the exclusion criteria for both groups of patients and the control group were:

Age < 18 years or age > 45 years, current pregnancy or lactation, chronic liver or kidney disease, history of any autoimmune disease (other than MS or NMOSD), abnormal thyroid function, history or therapy with agents known to be toxic to the reproductive system (including MS or NMOSD drugs, e.g., mitoxantrone and cyclophosphamide (Amato and Portaccio 2015)), current infertility treatment, history of polycystic ovary syndrome (PCOS), history of premature ovarian insufficiency (POI) (in the patient or a first-degree relative), irregular menstruation or any known endocrinopathies.

Data on disease-related factors including disease duration, history of medication use, and Expanded Disability Status Scale (EDSS) at the time of diagnosis and at the time of study and seronegative status (for NMOSD patients) was obtained from patients' medical records.

Other covariates, including demographics, age, body mass index (BMI), and nicotine consumption, were collected.

All participants gave written informed consent. All experiments carried out were approved by the ethics committee of Isfahan University of Medical Sciences (the study code of 396539) and in accordance with the Code of Ethics of The World Association (Declaration of Helsinki).

### Sample Collection and Enzyme-Linked Immunosorbent Assay Experiments

Serum samples were collected from the patients and the controls in the present study and stored at  $-20\text{ }^{\circ}\text{C}$ . The samples were brought to room temperature immediately before hormone measurements. A Sandwich Enzyme-Linked Immunosorbent Assay (ELISA) kit (AMH Gen II ELISA, Beckman Coulter, Webster, USA) was used to measure AMH. The process was according to the manufacturers' protocols.

### Statistical Analyses

Between-group comparisons were performed using one-way ANOVA, independent samples *t* test, Pearson's correlation coefficient, Spearman's correlation coefficient, and Mann-Whitney test. Statistical analyses were performed using IBM SPSS Statistics V23.0 (SPSS Inc., Chicago, IL, USA). In all experiments, a  $p < 0.05$  was defined as statistically significant.

## Results

### Demographic and Clinical Data

The present study included 69 women, 23 were diagnosed with MS, 23 were diagnosed with NMOSD, and 23 were healthy controls (HCs). The three groups were age-matched ( $29.69 \pm 5.21$  in MS patients,  $33 \pm 7.27$  in NMOSD patients, and  $30 \pm 4.84$  in healthy controls,  $p = 0.117$ ). BMI did not differ significantly between MS and NMOSD patients

( $23.22 \pm 4.03$  in MS patients vs.  $25.22 \pm 4.89$  in NMOSD patients,  $p = 0.138$ ). No one in the three groups smoked.

The mean for disease duration did not differ significantly between RRMS and NMOSD patients (3.39 years in MS patients vs. 3.91 years in NMOSD patients,  $p = 0.569$ ). The mean annualized relapse rate (ARR) was analyzed between the two groups of patients, which revealed a significantly higher mean for ARR in NMOSD patients ( $p = 0.049$ ). Mean EDSS at the time of diagnosis and at the time of the study were significantly higher among patients with NMOSD ( $p < 0.001$ ). Information on the demographic and clinical data is summarized in Table 1.

### Disease-Specific Characteristics of Patients with MS

The mean EDSS at the time of diagnosis was 1.41 (range, 0–4). The mean EDSS at the time of the present study was 0.21 (range, 0–1). The mean duration of the disease was  $3.39 \pm 0.55$  years, ranging from 1 to 9 years. The mean of ARR was 0.36, ranging from 0 to 2. Multiple Sclerosis Severity Scores (MSSS) (Roxburgh et al. 2005) was ranging from 1 to 3, with a mean of 1.3. Of the total of 23 patients with RRMS, 21 (91.3%) were currently under treatment with first-line disease-modifying drugs (DMDs), 18 (85.71%) with injectable DMDs, and 3 (14.2%) with oral DMDs (teriflunomide). From the former group of patients, eight had been receiving 44 mcg of subcutaneous interferon beta 1-a (ReCiGen) three times per week for a mean duration of 3.2 years. Thirty micrograms of intramuscular interferon beta 1-a (CinnoVex) was used once weekly by seven of the patients for a mean duration of 3.25 years. Three patients were under treatment with 0.25 mg of interferon beta 1-b (Betaferon) subcutaneously every other day for a mean duration of 2.6 years. The remaining three who were treated with DMDs, were under treatment with oral teriflunomide (Tebazio), 14 mg daily for a mean duration of 2.6 years.

Two of the patients (8.69%) who were not under treatment with DMDs at the time of the study, were being treated with rituximab — a monoclonal antibody (mAb). A dose of 1000 mg of the drug was administered intravenously (IV) every 6 months to these patients during a mean of 5 years.

**Table 1** Demographic and clinical data of the participants in the present study

	Age	AMH	BMI	Disease duration	Mean ARR	Mean EDSS (at diagnosis)	Mean EDSS (at study time)
RRMS	$29.7 \pm 1.08$	$3.59 \pm 0.55$	$23.22 \pm 0.84$	$3.39 \pm 0.55$	0.36	$1.41 \pm 0.23$	$0.21 \pm 0.08$
NMOSD	$33 \pm 1.52$	$3.66 \pm 0.61$	$25.22 \pm 1.02$	$3.91 \pm 0.72$	0.65	$2.69 \pm 0.24$	$2.17 \pm 0.35$
Control	$30 \pm 1.01$	$3.60 \pm 0.50$	-	-	-	-	-
<i>p</i> value	0.117	0.996	0.138	0.569	0.49	< 0.001	< 0.001

RRMS, relapsing-remitting multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; AMH, anti-Müllerian hormone; BMI, body mass index; ARR, annualized relapse rate; EDSS, Expanded Disability Status Scale

This group had a history of treatment with DMDs at some point in the disease duration before rituximab.

### Disease-Specific Characteristics of Patients with NMOSD

The mean EDSS at the time of diagnosis was 2.70 (range 0–6). The mean EDSS at the time of the present study was 2.17 (range 0–7). The mean duration of the disease was  $3.91 \pm 0.72$  years ranging from 1 to 12 years. The mean of ARR was 0.65, ranging from 0 to 2. While sixteen patients with NMOSD (78.27%) were under treatment with rituximab at the time of the study, seven (21.73%) were being treated with azathioprine (AZT). The former group of patients was receiving rituximab with a dose of 1000 mg IV every 6 months for a mean of 3.8 years. The latter group was receiving a mean dose of 150 mg azathioprine orally every day for a mean duration of 1.28 years. Only seronegative NMOSD patients were included in the present study.

### Serum AMH Levels

One-way ANOVA analysis showed no significant difference in mean AMH levels between the three groups. The mean AMH was  $3.59 \pm 0.55$  ng/ml in the RRMS group,  $3.66 \pm 0.61$  in the NMOSD group, and  $3.60 \pm 0.50$  ng/ml in healthy controls ( $p = 0.996$ ).

The cut-off value of  $\leq 0.4$  ng/ml was chosen for AMH as a predictor for fertility in in vitro fertilization (IVF). Lower levels of AMH are considered “extremely low” (Gnoth et al. 2008; Łukaszuk et al. 2014). None of the healthy controls fell into this category. Three patients in the MS group (13.4%), as well as three in the NMOSD group (13.4%), were among those with extremely low levels of AMH. More details about these patients are summarized in Table 2.

There was no significant correlation between serum levels of AMH and BMI among the two groups of patients ( $p = 0.138$ ). We found lower levels of AMH to be negatively associated with ARR (in both groups of patients) and MSSS, but the difference was not significant ( $p$  of ARR in RRMS patients = 0.27,  $p$  of ARR in NMOSD patients = 0.25,  $p$  of MSSS = 0.241). Serum levels of AMH among patients with NMOSD were negatively associated with disease duration ( $r = -0.42$ ,  $p = 0.023$ ).

Although mean serum levels of AMH had no significant correlation with EDSS at the time of diagnosis or at the time of study in RRMS group, a significant negative correlation was found in NMOSD group: higher EDSS at the time of diagnosis and the time of the study was associated with lower AMH ( $r = -0.402$ ,  $p = 0.03$ , and  $r = -0.457$ ,  $p = 0.014$ , respectively).

**Table 2** Cases of neuromyelitis optica spectrum disorder (NMOSD) and relapsing-remitting multiple sclerosis (RRMS) with very low and low levels of anti-Müllerian hormone (AMH)

Case	Age	Disease duration (year)	EDSS (at diagnosis)	EDSS (at study time)	Current treatment	Duration of current therapy (year)	Prior treatment and duration	AMH level (ng/ml)
NMOSD	42	1	7	4	AZT	1	AZT	0.1
NMOSD	44	12	4	3	AZT	7	Interferon beta-1a (CinnoVex)	0.1
NMOSD	44	12	6	3	AZT	12	AZT	0.2
RRMS	30	1	3	1	Interferon beta-1a (CinnoVex)	1	Interferon beta-1a (CinnoVex)	0.3
RRMS	32	1	2	0	Interferon beta-1a (CinnoVex)	1	Interferon beta-1a (CinnoVex)	0.3
RRMS	35	7	2	0	Interferon beta-1a (CinnoVex)	7	Interferon beta-1a (CinnoVex)	0.2

AZT, azathioprine



## Discussion

In the current study, it was demonstrated that serum AMH level was not significantly different in MS or NMOSD patients compared with that in healthy controls. With age acting as an important confounder, the age between the three groups included in the present study was matched. However, the ovarian reserve still decreased in each group, with an increase in participants' age. This is in line with the physiology of reproductive aging and though inevitable.

Inflammation in MS is mainly restricted to CNS structures (Thöne et al. 2015). From this perspective, lowering of ovarian reserve preceded by impaired fertility due to the disease itself seems unlikely. Sepúlveda et al. reported the ovarian reserve, assessed by biochemical and ultrasound imaging markers in MS patients, was not different from the healthy controls. No significant difference was found in mean serum AMH levels between RRMS patients and the healthy control group in the present study as well. They also found a poorer ovarian reserve to be associated with higher disease activity evaluated by ARR (Sepúlveda et al. 2016). Although a negative association of AMH levels with both ARR and MSSS was noticed in the present study, it was not significant.

Thöne et al. (2015) have previously reported serum AMH levels to be significantly lower among RRMS patients compared with that in HCs and hypothesized higher prevalence of POI among MS patients as a possible mechanism behind their results. The present study excluded patients with menstrual irregularities along with those diagnosed with POI or who had a first-degree relative who was previously diagnosed with POI in order to address this side as much as possible (Chapman et al. 2015). Nonetheless, FSH levels as a diagnostic test for POI were not measured in any of the two studies (Arora and Polson 2011).

Unlike the findings of the present study, the first case series of women with NMOSD showed lower mean AMH compared with HCs (Thöne et al. 2018). In their study, 78.6% of the patients recruited were positive for antibodies to AQP-4. AQP-4 has been identified in tissues other than CNS such as the kidney, lung, stomach, skeletal muscle (Verkman et al. 2011), uterus, and cervix (Huang et al. 2006). However, the ovary is not among the tissues identified for having AQP-4 though a diminished ovarian reserve due to an NMO-IgG-dependent inflammatory process is not expected. Yet patients included in the present study were all negative for AQP-4 abs.

A non-significant difference in EDSS severity was reported between patients with AMH levels lower than 0.8 ng/ml and those with normal levels of AMH in a previous study (Thöne et al. 2018). A significant negative correlation between EDSS severity (both at the time of diagnosis and at the time of the study), disease duration, and serum AMH was found in the current study. Also, a negative association of AMH with ARR was noted, which was not significant. Although the reason

behind these findings is not clear, it may suggest a higher disease activity, and inflammation leads to some degree of ovarian impairment.

In NMOSD patients with diencephalic (thalamic or hypothalamic) lesions, some endocrinopathies were reported that could potentially lead to fertility issues. Hyperandrogenism, amenorrhea, and central hypothyroidism are among these endocrinopathies (Mikhael et al. 2019; Pittock and Lucchinetti 2016). To focus more on the possible role of the disease itself on ovarian reserve and fertility, patients with any known endocrinopathies, including those mentioned above, were excluded from the present study.

To minimize the effect of medications used by patients (MS and NMOSD) on fertility markers, those who had ever received second-line disease-modifying drugs such as mitoxantrone and cyclophosphamide which were reported to have adverse effects on female fertility were excluded (Amato and Portaccio 2015; Cocco et al. 2008; Le Page et al. 2011; Portaccio et al. 2003). The present study only included those who received Interferon beta, Teriflunomide, azathioprine, and rituximab with which no effects on fertility to the date of this article were reported (Amato and Portaccio 2015; Leroy et al. 2015; Pendergraft et al. 2013). Nevertheless, future studies are recommended to be conducted with medication-naïve patients to further minimize the possible effects of drugs.

The small sample size limited the present study. Also, the present study included patients who were already under treatment, which makes speculating the exclusive role of the disease on fertility challenging. Excluding patients with known comorbidities may have led to a biased selection. Furthermore, the use of AMH as a predictor for natural fertility in other contexts than in vitro fertilization (IVF) has been limited (Dewailly et al. 2014). The present study was focusing on evaluating fertility based on the level of serum AMH. However, the evaluation of fertility is a way more complex subject with many aspects. One of the aspects that were not addressed in the present study was the role of endocrine pattern changes in women affected by MS. Some studies have tried to shed light on endocrine changes. They reported significantly higher levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, androstenedione, and total and free testosterone (Amato and Portaccio 2015; Cavalla et al. 2006; Grinstead et al. 1989). Moreover, the present study only included seronegative NMOSD patients, which raises the question of definite diagnosis and whether the patients were indeed NMOSD patients.

Studies should be conducted with larger sample sizes and more variables (including hormones with potential effects on fertility) affecting fertility in women with either RRMS or NMOSD to put an end to the controversial issue of fertility.

The present investigation was, to our knowledge, the second fertility study of female NMOSD patients that used AMH as a marker for ovarian reserve and had a larger sample size

than the previous investigation. Also, it was the first fertility study of Iranian patients with MS and NMOSD.

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## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Ethical Approval** All participants gave written informed consent. All procedures performed were approved by the ethics committee of Isfahan University of Medical Sciences (the study code of 396539) and in accordance with the ethical standards of the institutional and/or national research committee and with the Code of Ethics of The World Association (Declaration of Helsinki) and its later amendments or comparable ethical standards.

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