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Multiple sclerosis and fecundity: a study of anti-mullerian hormone level in Egyptian patients

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Abstract

Background Multiple sclerosis (MS) is a neurological disease that affects people aged 20–40 years on average. It classically affects young females of reproductive age. The prevalence of MS for females to males has increased markedly in recent years (from 2.3 to 3.5:1). Females with MS seem to use infertility treatments more frequently and fecundity could be affected years before making an MS diagnosis. The anti-Müllerian hormone (AMH) level is the strongest marker of ovarian reserve. Although recent studies suggest that patients with MS have lower ovarian reserve, there is no definite data to conclude that females with MS suffer from impaired fertility. This study aimed to investigate fertility and fecundity among female patients with MS by assessing AMH level. This study included 100 patients with MS and 60 healthy controls (HC). Both groups were assessed for AMH levels, activities of daily living (ADL) were assessed using the Kurtzke Expanded Disability Status Scale (EDSS) and the reproductive history of both groups was assessed via a self-administered questionnaire.

Results AMH levels among the HCs (0.34–2 ng/ml with a mean of 1.03 ± 0.41 ng/ml) were significantly higher than in patients with MS (0.15–2 ng/ml with a mean of 0.68 ± 0.31 ng/ml). The use of disease-modifying therapies (DMT) was the only predictor of below normal AMH among patients, but there was no significant correlation with age, duration of disease or type of DMT.

Conclusions Levels of AMH were significantly lower in MS patients than in healthy controls.

Keywords Multiple sclerosis, AMH, Fertility

Introduction

Multiple sclerosis (MS) is an autoimmune inflammatory disease of the central nervous system (CNS), most cases receive a diagnosis of MS between 20 and 40 years old, females are at more risk with a female to male ratio of 3:1 [1].

The data about fertility in females with MS is scarce. Women with MS often use different treatments for infertility, and fecundity can be affected years before an MS diagnosis [2]. Still, the reasons behind infertility among females with MS cannot be clearly determined, it may be due to disease-related pathology, drugs effect on endocrine and ovary function, or it may be due to MS patients avoiding getting pregnant [3].

Deterioration of ovarian reserve may affect fecundity [4]. Diminished ovarian reserve refers to females whose response to ovarian stimulation is reduced compared

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with females of same age [5]. Anti-Müllerian hormone (AMH) level is considered the most reliable marker of ovarian reserve [6].

The aim of this study was to assess ovarian reserve and fertility in MS patients by assessing the AMH serum level and comparing it to the serum AMH level of age-matched healthy controls (HC), and to study the relationship between AMH level on one hand and the use of different disease-modifying therapies (DMTs) and different aspects of MS disorder on the other hand.

Methods

This was a cross-sectional analytical study conducted on 100 reproductive-aged women (18–40 years) with any type of MS fulfilling revised McDonald criteria 2017 [7] and 60 healthy female controls of the same age. Participants were recruited from patients admitted to the Neurology department and/or patients attending Kasr Al Ainy MS Clinic during the period from January 2022 to July 2022. Females who were currently pregnant or lactating, females with chronic liver or kidney disease, females with abnormal thyroid function or autoimmune diseases other than MS, females on hormonal stimulation, fertility treatments or steroids, all were excluded from inclusion in this study.

The protocol for this study approved by the institutional review board of faculty of medicine—Cairo university (MD-104-2021) and a written informed consent was collected from all study subjects.

All participants underwent full clinical assessment including detailed history and neurological examination, Expanded Disability Status Scale (EDSS), history of relapses and DMTs.

All participants completed a questionnaire about their gynecological and obstetrical history, including age of menarche, menstrual cycles, dysmenorrhea, history of polycystic ovary (PCO), pregnancies and their outcomes, contraception, history of infertility and infertility treatment if needed, desire for a child and fear of being infertile.

Blood samples for AMH were collected. AMH measurement was done using an enzymatically amplified two-site immunoassay (Human Anti-Mullerian hormone, AMH ELISA Kit—Sunlong Biotech Co. Ltd.) with assay range: 0.5–25 ng/ml, sensitivity: 0.1 ng/ml, standard: 27 ng/ml. Values less than 0.4 ng/ml were considered to reflect a markedly diminished ovarian reserve. This AMH cut-off value was considered a good marker of poor response to ovarian hyperstimulation [8].

Data were analyzed by statistical package for social sciences (SPSS) version 28 (IBM Corp.). An exact test was used when expected frequency was less than 5 [9]. Logistic regression was used to identify independent predictors of AMH levels below 0.8 [10]. P-values less than 0.05 were considered statistically significant.

Results

The mean age for the patients' group was 28.8 ± 6.44 years and 27.63 ± 3.02 years for the HCs group (p-value 0.115). 57% of the patients' group were married, while only 11.7% of the HCs were married ($p < 0.001$). Five patients were divorced, and 2 patients were widowed at time of reporting, however, these patients were sexually active at some point during their disease course making the total number of sexually active patients 64 patients (57 married, 5 divorced and 2 widowed). The mean body mass index (BMI) for the patients' group was 25.9 ± 3.78 and 25.94 ± 2.32 for the HCs group (p-value 0.949).

As regards the type of MS; 82 patients had relapsing remitting MS (RRMS), 10 patients had secondary progressive MS (SPMS), 3 patients had primary progressive MS (PPMS) and 5 patients had clinically isolated syndromes (CIS). The mean age of onset was 24.29 ± 6.31 years with a mean disease duration of 55.3 ± 47.07 months. The mean EDSS was 2.18 ± 1.78. 34% of patients were on interferon beta, 22% were on fingolimod, 15% were on di-methyl fumarate, 13% were on other DMTs and 16% were on no DMT.

The mean age of menarche was 13.13 ± 1.28 years for the patients' group and 12.77 ± 0.81 years for the HCs (p-value 0.029). The mean AMH level among patients' group (0.68 ± 0.31 ng/ml) was significantly lower than HCs (1.03 ± 0.41 ng/ml) (< 0.001). Table 1 shows the AMH status and serum level stratification among patients and HCs. Table 2 summarizes the reproductive and gynecological history of patients and healthy controls.

There was no statistically significant difference between patients receiving different types DMTs as regards the level of AMH (p-value 0.437). However, when comparing RRMS patients receiving DMTs to patients on no DMT there was a statistically significant difference as regards AMH serum level, where RRMS patients on DMT were more likely to have very low (< 0.4 ng/ml) and low (< 0.8 ng/ml) AMH serum level than patients on no DMT (p-value 0.012) as shown in Table 3.

The use of DMT was the only statistically significant predictor of low AMH level (< 0.8 ng/ml) by using logistic regression analysis (p-value 0.013) as shown in Table 4, and it was highly statistically significant by using forward conditional regression ($p = 0.008$, OR: 4.545, 95% CI [1.477, 13.985]).

Table 1 AMH status among patients and healthy controls

		Patients' group		Healthy controls		P Value
		n	%	n	%	
AMH status	Abnormal AMH level (< 0.8 ng/dl)	68	68.0	20	33.3	< 0.001*
	Normal AMH level (> 0.8 ng/dl)	32	32.0	40	66.7	
AMH serum level stratified	very low AMH < 0.4 ng/ml	16	16.0	1	1.7	< 0.001*
	low AMH (0.4–0.8) ng/ml	52	52.0	19	31.7	
	normal AMH > 0.8 ng/ml	32	32.0	40	66.7	

AMH anti-müllerian hormone, *N* number, % percentage

* (P < 0.05) is statstically significant

Table 2 Reproductive and gynecological history of patients and healthy controls

		Patients' group		Healthy controls		P value
		n	%	n	%	
History of pregnancy	Yes	46	46.0	7	11.7	< 0.001*
	No	54	54.0	53	88.3	
History of infertility	Yes	6	6.0	0	0.0	0.083
	No	94	94.0	60	100.0	
Fears regarding fertility	Yes	72	72.0	55	91.7	0.005*
	No	28	28.0	5	8.3	
Contraception	Yes	37	37.0	5	8.4	< 0.001*
	No	63	63.0	55	91.7	
Menstrual irregularity	Yes	6	6.0	3	5.0	1
	No	94	94.0	57	95.0	
Dysmenorrhea	Yes	15	15.0	4	6.7	0.015*
	No	85	85.0	56	93.3	
History of PCO	Yes	5	5.0	1	1.7	0.409
	No	95	95.0	59	98.3	

PCO polycystic ovary, *N* number, % percentage

* (P value < 0.05) is statstically significant

Table 3 Effect of DMT on AMH Level

	RRMS patients receiving DMT		Patients on No DMT		P value
	n	%	n	%	
Very low AMH < 0.4 ng/ml	15	18.3	0	0.0	0.012*
Low AMH (0.4–0.8) ng/ml	45	54.9	6	37.5	
Normal AMH > 0.8 ng/ml	22	26.8	10	62.5	

RRMS relapsing remitting multiple sclerosis, *DMT* disease modifying therapies, *AMH* anti-müllerian hormone, *N* number, % percentage

* (P < 0.05) is statstically significant

Discussion

Due to the increasing incidence of MS among females, and the increasing number of treatments, the issue of fertility among females with MS has become extremely important [11, 12].

Plasma AMH level is the most reliable marker for ovarian aging in females. AMH plasma level starts to drop as soon as ovarian aging start. On the other hand, estrogen and progesterone levels may drop late in the perimenopausal or even the postmenopausal phase. AMH levels can predict the age of menopause as they strongly correlate with oocyte and leukocyte telomere lengths and antral follicle counts [13].

An important advantage of relying on AMH as a marker of ovarian reserve is that sample collection can be carried out anytime during the menstrual cycle because AMH level is considered rather stable across the menstrual cycle, unlike follicular stimulating hormone (FSH), estrogen and progesterone levels that fluctuate during different phases of menstrual cycle [14].

This study was designed as a cross-sectional analytical study investigating the reproductive history and

Table 4 Predictors of AMH level below 0.8 ng/ml using logistic regression analysis

		P value	OR	95% C.I	
				Lower	Upper
AMH level < 0.8 ng/ml	Age	0.263	0.951	0.871	1.038
	Smoking	1.000	0.000	0.000	
	BMI	0.244	1.091	0.943	1.262
	Age of menarche	0.111	0.721	0.482	1.078
	Dysmenorrhea	0.575	0.695	0.194	2.485
	Use of contraception	0.861			
	EDSS	0.563	0.877	0.561	1.369
	Disease duration (months)	0.160	1.010	0.996	1.024
	Current use of DMT	0.013*	5.392	1.436	20.243

OR odds ratio, *CI* confidence interval, *AMH* anti-müllerian hormone, *BMI* body mass index, *EDSS* expanded disability status scale, *DMT* disease modifying therapies

* ($P < 0.05$) is statstically significant

AMH serum level of a group of female MS patients and comparing them to a group of HCs of the same age, aiming to answer the question: "Does MS affect fertility of women with MS?".

In this study, AMH level among MS patients was significantly lower than among HCs ($p < 0.001$). These results are consistent with those of Thöne and colleagues who reported that AMH levels were lower in women with MS of reproductive age proposing an independent role for the disease in fertility [3].

On the other hand, several studies found that AMH levels did not vary between MS patients and healthy controls [6, 14–16]. Henes and colleagues stated that although ovarian reserve can be diminished in autoimmune disorders, it is unlikely that infertility due to diminished ovarian reserve is secondary to autoimmune disease pathology [17].

In this study, the level of AMH was not significantly correlated to disability or disease severity as measured by EDSS (p-value 0.56). Such findings agree with those of Thöne and colleagues who did not find a significant difference in EDSS between patients with AMH levels lower than 0.8 ng/ml and those with normal AMH levels [18].

Sepulveda and colleagues found that higher disease activity was associated with lower AMH levels [6]. Also, Graves and colleagues found that low AMH concentrations were strongly associated with increased disability in more than 400 women with MS. They concluded that their results implicated reproductive aging as a main factor leading disability progression in MS female patients, and perimenopause might be a risk factor for conversion to progressive disease [19].

In our cohort, there was no statistically significant correlation between low serum AMH (below 0.8 ng/ml) and disease duration (p-value 0.16), age of menarche (p-value 0.11), BMI (p-value 0.24), age (p-value,0.26), smoking (p-value 1.0), use of contraception (p-value 0.86) and dysmenorrhea (p-value 0.58).

Different cohorts yielded different results as regards factors affecting AMH level. Sadeghpour and colleagues found a significant negative correlation between disease duration and serum AMH levels [15]. Other multicenter studies looking into the relation between BMI and AMH levels of patients with PCOs, revealed that the higher the BMI the lower the AMH regardless patients' age, race, site and smoking status [20, 21].

There is scarce information on the influence of DMT on fertility in humans [22]. In the current study, it was found that the use of DMT was the only predictor of below-normal AMH serum level (< 0.8 ng/ml) among MS patients (p-value 0.013) by using logistic regression analysis, and it was highly statistically signification by using forward conditional regression (p-value 0.008).

In their cohort, Thöne and colleagues found that having MS and being currently not treated with any DMT were the only significant predictors for very low AMH levels. They concluded that the use of DMT to modulate disease activity in MS indicates that the benefits of suppressing disease activity in MS outweigh the potential negative effects of DMT on ovarian reserve [3].

The relationship between MS and infertility is not fully understood, but a link seems to exist between progression, severity of disease and infertility [16].

This study showed that 72% of patients had fears regarding their fertility and MS's effect on fecundity, and 21% of patients decided to have a second child after being diagnosed with MS. Lavorgna and colleagues conducted an online survey in 2019, which showed that 33 out of 395 participants never wanted to become a parent because of MS "anti-parenthood after diagnosis" while

362 were in favor of parenthood. The frequency of a second child in patients with MS after diagnosis was 38% compared to 67% in people without MS diagnosis [23].

Educating patients is of extreme importance in this aspect. Patients should be aware of the reduced disease activity during pregnancy and the fact that certain classes of DMTs can be used safely during pregnancy and lactation. Most MS patients fearing pregnancy are unaware of these facts and accordingly may attempt to avoid or delay pregnancy. Also, patients should be educated about the importance of planning pregnancy in advance and coordinating treatment plans with the physician following the case.

There are no studies directly assessing pregnancy success rates in MS [24, 25]. However, some studies showed that females with MS may have fewer children as compared to general population [23]. In the current study, it was found that 54 out of 64 sexually active patients (84%) got pregnant and only one patient complained from 1ry infertility.

The effect of MS on fecundity on MS could be due to the effect of disease on fertility, the effect of symptoms such as sexual dysfunction, bladder dysfunction and fatigue on trying to get pregnant [26].

Several limitations to be taken into consideration. First, the AMH level needs to be empowered with antral follicle count to surely help in the diagnosis of ovarian aging. Second, the patients' sample was predominantly RRMS patients, with other MS subtypes under-represented with insufficient numbers to draw statistically significant conclusions subtypes other than RRMS. Third, both study groups were mismatched as regards marriage status. Lastly, we did not address the relation of DMT to fertility in women with MS—specially RRMS—in detail, but we notice the correlation and we aim to emphasis more and more on this topic in further research. Despite these limitations, to our knowledge, this is the first study to address this issue in Egypt.

Conclusions

Multiple sclerosis may affect female fertility and fecundity by affecting ovarian aging and decreasing AMH levels.

Abbreviations

MS	Multiple sclerosis
AMH	Anti-müllerian hormone
HC	Healthy controls
DMT	Disease-modifying therapies
CNS	Central nervous system
PCO	Polycystic ovary
C	Degree Celsius
g	Relative centrifugal force
ELISA	Enzyme-linked immunosorbent assay
OR	Odds ratio
CI	Confidence interval
FSH	Follicular stimulating hormone

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Author contributions

MAZ, GR, SA, SAS, MIH, EM, IF & LE carried out the work. MAZ, GR & MIH designed the protocol. SA, SAS, EM & LE shared collected scientific data. SA, GR & MIH was responsible for writing the initial draft of the manuscript. SA, EM, IF & LE did the statistical analysis. All authors read and approved the final manuscript.

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Availability of data and materials

The data sets generated and/or analyzed during the current study are not publicly available due to the current Egyptian clinical research legislation but are available from the corresponding author on reasonable request and after institutional approval.

Declarations

Ethics approval and consent to participate

The authors obtained permission to conduct this study that was approved by the Institutional Review Board (IRB), Faculty of Medicine—Cairo University (MD-104-2021). All participants signed an informed consent. The procedures followed were in accordance with our protocol. We recruited 60 controls and 100 patients from Kasr Al Ainy Multiple Sclerosis Clinic.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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