Ovarian reserve in patients with ankylosing spondylitis

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Abstract

Purpose The aim of this study was to determine the autoimmune effects of ankylosing spondylitis (AS) on the fertility potential of women by evaluating ovarian reserves of AS patients.

Methods A total of 104 patients, 52 in the AS group (study group) and 52 in the control group were included in the study. Ovarian reserve was evaluated by serum anti-Müllerian hormone (AMH) levels, antral follicle count (AFC) and baseline serum follicle-stimulating hormone (FSH) levels.

Results The mean serum AMH levels were significantly lower in the study group when compared to the controls (2.203 ± 1.110 vs. 1.188 ± 0.891, $p < 0.001$). In addition, the mean AFC was also significantly lower in the study group. (10.67 ± 1.81 vs. 9.54 ± 2.50, $p = 0.009$). Mean FSH levels were calculated to be 6.72 ± 1.14 in the study group and 7.21 ± 1.22 in the control group. The difference was not statistically significant ($p = 0.781$).

Conclusion This study shows that AS like several other autoimmune conditions has an adverse effect on the female fertility potential. Therefore, an early start and long-term management of AS patients who have fertility desire is recommended. Serum AMH levels can be used in monitoring ovarian reserve and in early detection of reproductive decline of AS patients.

ClinicalTrial Number NCT04209881.

Keywords Ankylosing spondylitis · Fertility · Antral follicle count · Anti-müllerian hormone · Ovarian reserve

Introduction

Female fertility is affected by genetic, endocrinological, environmental, psychological, and iatrogenic factors. Ovaries play two important roles in female fertility and their proper function is essential for a healthy female reproductive function. They produce mature eggs for fertilization and produce hormones essential for the menstrual cycle as well as for the maintenance of a pregnancy [1]. The adverse effects of autoimmune disorders on the ovarian function have already been reported [2]. An autoimmune etiology can be found in approximately one-third of the premature ovarian failure (POF) cases [3]. Furthermore, a condition called autoimmune oophoritis, where the immune system attacks the ovaries, develops in the presence of autoimmune polyendocrine syndromes [4].

Ankylosing spondylitis (AS) is characterized as an autoimmune and a chronic inflammatory disease. It primarily affects the axial skeleton. Involvement of peripheral joints as well as extra-articular manifestations is also observed. The mean age of diagnosis is within the reproductive years, commonly during late teens and early 20′s [5]. A prevalence ranging from 0.7 to 49 per 10,000 has been reported [6]. AS is associated with several autoimmune disorders, including inflammatory bowel disease, anterior uveitis and psoriasis, which indicates the possibility of a common genetic and pathophysiological basis. Furthermore, it has

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been reported that patients diagnosed with an autoimmune disorder develop another autoimmune condition with a risk of 25% [7]. According to literature, autoimmune disorders, such as rheumatoid arthritis, familial Mediterranean fever, systemic lupus erythematosus, autoimmune thyroiditis, and Sjögren's syndrome, reduce ovarian reserve, the capacity of ovaries to produce of eggs for fertilization [8–12].

Fertility potential can be characterized by the assessment of the ovarian reserve [13]. Ovarian reserve is determined by the antral follicle count (AFC), serum anti-Müllerian hormone (AMH) levels and basal follicle-stimulating hormone (FSH) levels [14, 15]. It is known that assessment of serum AMH levels in sub-fertile population has a high predictive value for fertility potential [16].

The adverse effects of several autoimmune disorders on the ovarian reserve have already been established. However, the effects of AS on the female fertility potential have not yet been evaluated. The aim of this study was to determine the autoimmune effects of AS on the fertility potential of AS patients by evaluating their ovarian reserves through determination of AFC, serum AMH levels and serum FSH levels.

Materials and methods

This prospective cohort study was conducted at the gynecological outpatient clinic of Health Sciences University Istanbul Kanuni Sultan Suleyman Training and Research Hospital, between June 2019 and January 2020. The study protocol was approved by the institution's Ethics Committee (2019/456 14.10.2019) and was registered to Clinical-Trials.gov (NCT04209881). Written informed consent was obtained from subjects before they were enrolled in the study.

52 patients who were diagnosed with AS according to the Modified New York criteria, who visited our gynecological clinic during the study period and who met the inclusion criteria were included in the study group [17]. Women with regular menstrual cycles (21–35 days), with cycle length variations of < 4 days, with both ovaries intact, non-smokers, who had no history of liver failure, malignant diseases, chronic renal failure, infertility or other gynecological conditions, such as abnormal uterine bleeding, and who had not been on hormonal or herbal medication during the previous 3 months met the inclusion criteria. Women diagnosed with other autoimmune and/or chronic inflammatory disorders were excluded from the study. 52 healthy patients who visited the gynecological outpatient clinic during the same period for routine gynecological control were included in the control group.

Patients' biometric data including age, body mass index (BMI), fertility and menstrual history were recorded. Venous blood samples were obtained during the follicular phase (days 2–6) of the menstrual cycle during the morning hours (08:00–09:00). Serum samples were stored at −20 °C and assayed for FSH, luteinizing hormone (LH), estradiol (E2), prolactin (PRL) and thyroid-stimulating hormone (TSH). Serum AMH levels were measured with fully automated AMH electrochemiluminescence assay (ECLIA; ElecsysVR AMH assay, Roche Diagnostics, Basel, Switzerland).

All patients received a thorough gynecological examination. The AFC was performed using transvaginal ultrasound by counting the antral follicles with a diameter of 2–10 mm. All AFCs were carried out by the same gynecologist who was blinded to the medical data of the patients. Ovarian volume was calculated using the formula postulated by Orsini et al. (length × width × thickness × 0.5235) [18].

Sample size calculations were performed according to an estimated prevalence of 0.5% for AS. The estimation was done based on the reported prevalence of 0.1–1.4% in the western countries [6]. A sample size of 51 was calculated with a 95% confidence interval and a 5% desired precision. Data analysis was performed using SPSS version 24.0 for Windows (SPSS Inc., Chicago, IL). Pearson normality test was used for the normality and the distribution of variables. Numerical variables were compared using the independent samples t test or the Mann–Whitney U test. The data are expressed using means with standard deviations. A p value of < 0.05 was considered statistically significant.

Results

A total of 104 patients, 52 in the AS group (study group) and 52 in the control group were included in the study. The demographic data of the patients are displayed in Table 1. There are no significant differences between the groups in

Table 1 Comparison of the demographic properties between the AS group and the control group

Demographic properties	Control group	AS (study) group	p value
Age (years)	29.62 ± 5.60	29.52 ± 5.48	0.930
Gravidity (n)	1.52 ± 0.80	1.40 ± 0.75	0.325
Parity (n)	1.12 ± 0.62	1.10 ± 0.60	0.460
BMI (kg/m^2)	22.61 ± 2.33	22.50 ± 2.47	0.810
FSH (mIU/ml)	7.21 ± 1.22	6.72 ± 1.14	0.781
LH (mIU/ml)	6.13 ± 0.92	6.29 ± 1.01	0.196
E2 (pg/ml)	67.79 ± 6.83	67.46 ± 6.79	0.137
TSH (mIU/ml)	1.93 ± 0.38	1.87 ± 0.30	0.148
PRL (ng/ml)	13.31 ± 3.15	12.83 ± 2.95	0.860
Time passed since diagnosis of AS (years)	–	5.04 ± 2.67	–

BMI body mass index; *FSH* follicle-stimulating hormone; *LH* luteinizing hormone; *E2* Estradiol; *TSH* thyroid stimulating hormone; *PRL* prolactin all values are given as median ± standard deviation

terms of age, BMI, and in the levels of follicular phase hormones (FSH, LH, E2 and PRL) and TSH. Therefore, the two groups are comparable in nature.

Mean serum AMH levels, mean AFC, and mean ovarian volumes are presented in Table 2. The mean ovarian volumes for both right and left ovaries were similar in both groups. However, the mean serum AMH levels were significantly lower in the study group when compared to the controls (2.203 ± 1.110 vs. 1.188 ± 0.891, $p < 0.001$). In addition, the mean AFC was also significantly lower in the study group. (10.67 ± 1.81 vs. 9.54 ± 2.50, $p = 0.009$). However, this difference in terms of AFC between the two groups did not reflect on to their clinical presentation. Both groups were clinically similar. Mean FSH levels were calculated to be 6.72 ± 1.14 in the study group and 7.21 ± 1.22 in the control group (Table 1). The difference was not statistically significant ($p = 0.781$).

Discussion

In the current study, the ovarian reserves of AS patients were assessed to determine whether AS had an adverse effect on the female fertility potential. Serum AMH level is proportional to the number of developing follicles and it is an indicator of the follicle pool. Therefore, it is commonly used to monitor ovarian reserve in patients who are at a higher risk for infertility, such as women with endometriosis [19]. Furthermore, a strong correlation between serum AMH levels and the AFC has already been reported [20, 21]. Therefore, serum AMH levels and AFC are commonly used in evaluating the ovarian reserve during fertility treatments [22]. Recent studies demonstrated that serum AMH levels are lower in women of reproductive age with autoimmune disorders [8–12]. The significantly low levels of serum AMH and AFC observed in the AS group of our study were in accordance with the literature and the results were interpreted as a reduction in the ovarian reserves of AS patients compared to the healthy subjects. The results indicated that the autoimmunity associated with AS, as with several other autoimmune disorders, has an adverse effect on the female ovarian function. Furthermore, in literature, AMH levels lower than 1.2 are accepted as low ovarian reverse [23].

Thus, these patients including the ones in our study group could be referred to oocyte or embryo cryopreservation.

In 4–30% of patients with an autoimmune disease, gonadal failure has been reported [24, 25]. Gooren et al. conducted a study with 22 male AS patients evaluating their testicular function. Reduced levels of testicular testosterone reserve, elevated levels of LH, inversion of estradiol testosterone ratio and slightly increased E2 levels were reported. The study showed the negative effects of AS related autoimmunity on the testicular function [26]. In a study conducted by Gooren et al., the differences in female sex hormones were reported between menstruating and menopausal patients with active and inactive AS. They reported that E2 levels in menstruating patients with active AS were significantly lower than those with inactive AS indicating that the increased autoimmunity during the active phase of the disease affects the hormonal regulation of women in reproductive ages negatively. The early onset of AS, and a commonly encountered fulminant course during pregnancy imply that sex hormones play a role in pathophysiology of AS [27].

Genetic background constitutes an important part in the pathogenesis of AS as well. One of the most important genetic factors associated with AS is the major histocompatibility complex (MHC) class I allele encoding human leukocyte antigen B27 (HLA-B27) [28]. Among first-degree relatives with positive HLA-B27, a higher prevalence has been observed [29]. Risk ratios of 94%, 25%, and 4% were calculated for first-, second-, and third-degree relatives, respectively [30]. Thus, the presence of AS in a first-degree relative puts one in a higher risk group. Since the clinical manifestations of autoimmunity occur after months or years of a subclinical course and since fertility is already affected at the subclinical stages, an early management of women in reproductive ages with autoimmune disorders has utmost importance [31, 32]. Therefore, women with AS positive mothers or siblings should be advised accordingly in terms of the risk factors on their fertility potential.

To the best of our knowledge, this is the first study evaluating the serum AMH levels and AFC in women with AS. The results show that serum AMH levels and AFC, in other words the ovarian reserves, of AS patients are affected negatively by the autoimmunity of AS. It is possible that autoimmune damage to the ovaries happens over the course of

Table 2 Comparison of serum AMH, AFC and ovarian volumes between the study and the control groups

	Control group	AS (Study) group	*p* value
AMH (ng/ml)	2.203 ± 1.110	1.188 ± 0.891	**< 0.001**
AFC (*n*)	10.67 ± 1.81	9.54 ± 2.50	**0.009**
RO volume (cm^3)	$11,470.32 \pm 3148.45$	$10,933.11 \pm 3763.06$	0.432
LO volume (cm^3)	$11,043.62 \pm 2773.94$	$10,490.18 \pm 2941.02$	0.326

AMH anti-Müllerian hormone; *AFC* antral follicle count; *RO* right ovary; *LO* left ovary all values are given as median ± standard deviation

the autoimmune condition. Thus, a progression to POF or early menopause might be possible. Therefore, long-term follow-up is advisable in these patients and serum AMH levels along with AFC can be used to monitor these patients over the course of their disease.

Conclusion

This study shows that AS like several other autoimmune conditions has an adverse effect on the female fertility potential through a reduction in the ovarian reserve, which can be determined by serum AMH levels and AFC. Therefore, an early start and long-term management of AS patients who have fertility desires are recommended. Serum AMH levels can be used in monitoring ovarian reserve and in early detection of reproductive decline of AS patients.

Compliance with ethical standards

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