

# Effects of chronic urticaria on ovarian reserve

✉ Mehmet Ak<sup>1</sup>, ✉ Mustafa Taş<sup>2</sup>, ✉ Hüseyin Aksoy<sup>1</sup>, ✉ Ragıp Ertaş<sup>3</sup>

<sup>1</sup>Department of Obstetrics and Gynecology, Kayseri City Hospital, Kayseri, Turkey

<sup>2</sup>Department of Obstetrics and Gynecology, Acibadem Kayseri Hospital, Kayseri, Turkey

<sup>3</sup>Department of Dermatology, Kayseri City Hospital, Kayseri, Turkey

Cite this article as: Ak M, Taş M, Aksoy H, Ertaş R. Effects of chronic urticaria on ovarian reserve. *J Health Sci Med.* 2023;6(4):772-774.

Received: 13.03.2023

Accepted: 02.07.2023

Published: 30.07.2023

## ABSTRACT

**Aims:** To evaluate the ovarian reserve in women with chronic urticaria (CU).

**Methods:** Thirty women with CU and twenty nine healthy controls were enrolled in this study. Serum levels of anti-Müllerian hormone (AMH), follicle-stimulating hormone (FSH), estradiol (E2), and luteinizing hormone (LH) were measured on cycle day 2. All patients underwent transvaginal ultrasonographic examination on the second day of their menstrual cycle to assess Antral Follicle Count (AFC) and ovarian volume (OV). The disease activity of CU was measured with the urticaria control test (UCT) and urticaria activity score (UAS).

**Results:** Women with CU had significantly lower concentrations of AMH, AFC, and E2 than controls. Additionally, total AFC and ovarian volume were significantly lower in women with CU than in the control group. UAS and UCT were positively associated with FSH and negatively associated with AMH, AFC, and OV.

**Conclusion:** This is the first prospective controlled study to examine ovarian reserve in women with CU. In this study, we found that ovarian reserve was significantly reduced in women with CU. CU may negatively affect the ovarian reserve but the mechanism of this effect is unclear.

**Keywords:** Antral follicle count, ovarian volume, anti-Müllerian hormone, chronic urticaria

## INTRODUCTION

Chronic urticaria (CU) is a chronic disease characterized by itchy wheals and flare-type skin reactions lasting more than six weeks.<sup>1</sup> The causes remain unknown, so it is considered idiopathic and occurs in about 0,75% of patients.<sup>2,3</sup> Generally, CU has an immunological and inflammatory process and may affect all organs.<sup>4</sup> There have been studies that found an association of CU with thyroid autoimmunity, which further supports its autoimmune origin.<sup>5</sup> In the literature, no study has examined the effects of CU on the ovary. The reproductive potential of women can be estimated with ovarian reserve tests consisting of basal levels of follicle-stimulating hormone (FSH), estrogen (E2), anti-Müllerian hormone (AMH), as well as antral follicle count (AFC) and ovarian volume (OV).<sup>6</sup> The use of multiple ovarian reserve markers suggests that no test is ideal. In fact, the biggest determinant of fertility potential in a regularly cycling woman is age.<sup>7</sup> However, the most widely used and reliable tests measuring ovarian reserve are AMH and AFC. A diminished ovarian reserve is defined as a reduced ability to produce eggs in the ovaries of a woman at any age.<sup>8</sup> Thus far, only one case

report found an association between CU and ovarian reserve.<sup>9</sup> Chronic diseases negatively affect the ovarian reserve of women and decrease their reproduction potential. The most commonly used tests, including AFC and AMH, may measure this effect of chronic diseases on ovarian reserve. In the literature, this is the first study to evaluate the effects of CU on ovarian reserve using both ultrasonographic and biological markers. The present study investigated the efficacy of the regularly used markers for predicting ovarian reserve in reproductive-age women with CU.

## METHODS

The study was carried out with the permission of Acibadem University Ethics Committee (Date: 22.11.2018, Decision No: 2018-18/29). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study was conducted in the Department of Obstetrics and Gynecology and Dermatology at Kayseri City Training and Research Hospital. Thirty women with

Corresponding Author: Mehmet Ak, ak-mehmet@hotmail.com



This work is licensed under a Creative Commons Attribution 4.0 International License.

CU and 29 healthy women as controls were admitted to this study. Female patients with a confirmed diagnosis of CU were asked to participate. After written consent was obtained, patients were screened for eligibility. The inclusion criteria were:

1. Reproductive age (20-30 years),
2. Regular menstruation cycle (interval of 21–35 days),
3. Less than 4 days of variation in cycle length, and
4. The presence of both ovaries.

The exclusion criteria were chronic kidney or liver failure, any known malignancy, smoking history, infertility, gynecological abnormalities including dysfunctional uterine bleeding or menorrhagia, previous ovarian surgery, use within the last 3 months of a hormonal preparation or unregulated herbal product, or a polycystic ovary syndrome (PCOS) diagnosis. The control group was selected from women attending their routine gynecological exam without any complaints (for example, yearly pap smear screening). Patients with CU were diagnosed in the Department of Dermatology. In the early follicular phase of the menstrual cycle (days 2–4), all patients had a venous blood sample taken between 08:00 am and 09:00 am from the antecubital region. The enzymelinked immunosorbent assay (ELISA) method was used to measure the levels of folliclestimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), and AMH. The AMH Chemiluminescent Microparticle Immunoassay Model 602 (Cobas®, Roche, Mannheim, Germany) was used to assess the AMH levels. The Photometric Model 702 (Cobas®, Roche, Mannheim, Germany) was used to analyze FSH, LH, E2, and PRL levels. A pelvic ultrasound was used to measure ovarian volume and AFC on the same day as the blood draw. The same operator blinded to all patient information performed a pelvic ultrasound with a 7.5 MHz transvaginal probe to count the total number of antral follicles measuring 2–10 mm in diameter. Ovarian volume was calculated using the equation of an ellipsoid (0.526 x length x height x width) (10). Participants' height, weight, body mass index (BMI), disease duration, and age were noted. After the venous blood samples were taken, they were stored at -20±8 °C and assayed for LH, FSH, E2, and AMH. The disease activity of CU was measured using the urticaria control test (UCT) and urticaria activity score (UAS). The same author, R.E., evaluated all participants and the severity of the disease was scored from 0 (no symptoms) to 10 (highest symptoms) using a visual analog scale (11).

**Statistical Analysis**

Mean±standard deviation (SD) was used to report numerical variables. The Kruskal-Wallis test and Mann-Whitney U test were used to analyze non-normally distributed variables. For normally distributed data, paired t-tests were used to compare the groups. Relationships between parameters were assessed using

Spearman correlation coefficients. p<0.05 was considered statistically significant. The Statistical Package for the Social Sciences, version 15.0 (SPSS, Chicago, IL, USA), was used to perform all analyses.

**RESULTS**

**Table 1** shows the summary of demographic measurements of the CU and control groups. No significant differences were found between the groups for age, BMI, and LH. FSH was significantly higher in the CU group than in the control group (8.8±4.06 vs. 8.0±0.84, p=0.001).

**Table 1.** Demographic characteristics and hormonal levels of the participants

	Patient (n:30)	Control (n:29)	p-value
Age	23.26±7.89	24.24±2.01	0.44
BMI (kg/m <sup>2</sup> )	23.96±3.78	23.07±0.84	0.216
FSH (mIU/mL)	8.8±4.06	8.0±0.84	0.001
LH (mIU/mL)	7.27±3.62	7.0±0.88	0.09
E2 (pg/mL)	45.93±21.37	59.62±3.26	<0.001
Total AFC	9.2±3.5	12.5±1.5	<0.001
Total OV (cm <sup>3</sup> )	7.7±4.21	14.37±1.49	<0.001
AMH (ng/ml)	1.62±1.13	2.51±0.50	<0.001

BMI: Body mass index, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, E2: Estradiol, AFC: Antral follicle count, OV: Ovarian volume, AMH: Anti Müllerian hormone.

The values of E2, total AFC, OV, and AMH were significantly lower in the CU group than in the control. When we looked for correlations, UAS and UCT were positively associated with FSH and negatively associated with AMH, AFC, and OV (**Table 2**).

**Table 2.** Association of urticaria activity score (UAS) and urticaria control test (UCT) with hormonal levels.

	UAS	UCT	p-value
FSH	0.44	0.32	0.03
AMH	-0.27	-0.21	0.05
AFC	-0.28	-0.18	0.04
OV	-0.35	-0.27	0.66

FSH: Follicle-stimulating hormone, AMH: Anti-Müllerian hormone, AFC: Antral follicle count, OV: Ovarian volume. Statistical analysis was done by Spearman correlation coefficient.

**DISCUSSION**

Ovarian reserve is important to achieve pregnancy for reproductive-age women. Recently, the measurement of ovarian reserve has been used to predict the reproductive capacity of women. The most widely used tests are AFC and AMH.<sup>12</sup> This is the first study to evaluate the effects of CU on ovarian reserve and evaluate the associated hormones and AFC. Decreased levels of AMH, which is produced by granulosa cells, are considered a sensitive marker of diminished ovarian reserve. Decreased AFC is another sensitive marker to assess diminished ovarian

reserve.<sup>13</sup> In this study, we used the most predictive and widely used tests to predict ovarian reserve in women with CU. The values of AMH and AFC were significantly decreased in our study. Additionally, UAS and UCT are sensitive tests to measure the severity of CU. In our study, we first evaluated the correlation between the severity of CU and ovarian reserve tests. UAS and UCT were positively associated with FSH and negatively associated with AMH, AFC, and OV. Recent studies indicate that lower AMH levels may show an increased risk of earlier menopause.<sup>14</sup> Autoimmune chronic diseases such as systemic lupus erythematosus (SLE), Behçet, and others may negatively affect ovarian reserves.<sup>15-17</sup> Although the etiology is not clear for CU, the most common reason is autoimmune conditions. CU is also associated with chronic inflammation and the disease activity affects the organs.<sup>18</sup> In this study, we evaluated effects on reproductive health in women with CU compared to women without CU. In the present study, the activity of CU negatively affected the ovarian reserve. Therefore, treatment and duration of CU may be used to evaluate this negative effect of CU on ovarian reserve. The most important factors for fertility are the number and quality of antral follicles. The number of oocytes is positively correlated to pregnancy in infertility treatment.<sup>19</sup> Age is one of the most pivotal factors for oocyte quality.<sup>20</sup> In this study, the diminished values of AMH and AFC may prompt a discussion of fertility preservation for women with CU such as oocyte freezing.

## CONCLUSION

This is the first study to suggest that women with CU are more likely to have diminished ovarian reserves in their reproductive years than control women. Additional studies of women with CU using a larger sample size are needed to confirm that the disease activity negatively affects the ovarian reserve.

## ETHICAL DECLARATIONS

**Ethics Committee Approval:** The study was carried out with the permission of Acibadem University Ethics Committee (Date: 22.11.2018, Decision No: 2018-18/29).

**Informed Consent:** All patients signed and free and informed consent form.

**Referee Evaluation Process:** Externally peer reviewed.

**Conflict of Interest Statement:** The authors have no conflicts of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

**Author Contributions:** All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

## REFERENCES

- O'Donnel BF, Lawlor F, Simpson J, Morgan M, Greaves MW. The impact of chronic urticaria on quality of life. *Br J Dermatol*. 1997;136(2):197-201.
- Zuberbier T, Abdul Latiff AH, Abuzakouk M, et al. The international EAACI/GA<sup>2</sup>LEN/EuroGuiDerm/ APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. *Allergy*. 2022;77(3):734-766.
- Ertaş R, Özyurt K, Yıldız S, Ulaş Y, Turasan A, Avcı A. Adverse reaction to omalizumab in patients with chronic urticaria: flare up or ineffectiveness?. *Iran J Allergy, Asthma Immunol*. 2016;15(1):82-86.
- Ertaş R, Özyurt K, Karakükçü Ç, et al. Evaluation of platelet parameters and neutrophil/lymphocyte ratio during omalizumab treatment in patients with severe chronic spontaneous urticaria. *Turkish J Med Sci*. 2018;48(6):1255-1262.
- Eliakim R, Sherer DM. Celiac disease: fertility and pregnancy. *Gynecol Obstet Invest*. 2001;51(1):3-7.
- Tuğrul Ayanoglu B, Özdemir ED, Türkoğlu O, Alhan A. Diminished ovarian reserve in patients with psoriasis. *Taiwan J Obstet Gynecol*. 2018;57(2):227-230.
- Cakmak E, Karakus S, Demirpence O, Demet Coskun B. Ovarian reserve assessment in celiac patients of reproductive age. *Med Sci Monit*. 2018;24:1152-1157.
- Loverro G, Nappi L, Mei L, Giacomoantonio L, Carriero C, Tartagni M. Evaluation of functional ovarian reserve in 60 patients. *Reprod Biomed Online*. 2003;7(2):200-204.
- Ruggeri RM, Vita G, D'Angelo AG, et al. The unusual association of Graves' disease, chronic spontaneous urticaria, and premature ovarian failure: report of a case and HLA haplotype characterization. *Arq Bras Endocrinol Metabol*. 2013;57(9):748-752.
- Şahin A, Karakuş S, Durmaz Y, et al. Evaluation of ovarian reserve with anti-Müllerian hormone in familial Mediterranean fever. *Int J Rheumatol*. 2015;380354.
- Ertaş R, Erol K. The frequency of chronic widespread pain and its impact on quality of life in patients with chronic spontaneous urticaria. *Konuralp Med J*. 2019;11(1):101-105.
- Broer SL, Dölleman M, Opmeer BC, Fauser BC, Mol BW, Broekmans FJM. AMH and AFC as predictors of excessive response in controlled ovarian hyperstimulation: a metaanalysis. *Human Reproduction Update*. 2011;17(1):46-54.
- Reshef T, David BS. Ovarian reserve testing: a user's guide. *Am J Obstet Gynecol*. 2017;217(2):129-140.
- Kruszyńska A, Słowińska-Srzednicka, J. Anti-Müllerian hormone (AMH) as a good predictor of time of menopause. *Menopause Review/Przegląd Menopauzalny*. 2017;16(2):47-50.
- Henes M, Froeschlin J, Taran FA, et al. Ovarian reserve alterations in premenopausal women with chronic inflammatory rheumatic diseases: impact of rheumatoid arthritis, Behçet's disease and spondyloarthritis on anti-Müllerian hormone levels. *Rheumatology*. 2015;54(9):1709-1712.
- Carp HJ, Selmi C, Shoenfeld Y. The autoimmune bases of infertility and pregnancy loss. *J Autoimmunity*. 2012;38(2-3):266-274.
- Cutolo M, Straub RH. Sex steroids and autoimmune rheumatic diseases: state of the art. *Nat Rev Rheumatol*. 2020;16(11):628-644.
- Giménez Arnau AM, Grattan C, Zuberbier T, Toubi E. An individualized diagnostic approach based on guidelines for chronic urticaria (CU). *J Eur Acad Dermatol Venereol*. 2015;29 Suppl 3:3-11.
- Barbakadze L, Kristesashvili J, Khonelidze N, Tsagareishvili G. The correlations of anti-mullerian hormone, follicle-stimulating hormone and antral follicle count in different age groups of infertile women. *Int J Fertil Steril*. 2015;8(4):393-398.
- Ahmed TA, Ahmed SM, El-Gammal Z, et al. Oocyte aging: the role of cellular and environmental factors and impact on female fertility. *Cell Biol Translat Med Stem Cells Regenerat Med*. 2020;8:109-123.