European Review for Medical and Pharmacological Sciences 2023; 27: 4608-4613

# Evaluation of ovarian reserves in women suffering from an autoimmune disease vitiligo

Ö. ÜNAL, N. TÜTEN

Department of Gynecology and Obstetrics, Health Sciences University, Kanuni Sultan Suleyman Training and Research Hospital, Istanbul, Turkey

**Abstract. – OBJECTIVE: In this study, we aimed to investigate whether vitiligo, an autoimmune disease, affects the ovarian reserves of women suffering from this disease.**

**PATIENTS AND METHODS: This case-control study included 27 vitiligo patients and 44 healthy participants with regular menstrual cycles. The total number of participants was 71. We conducted the study in a tertiary hospital between June 2022 and November 2022. We carried out the study after receiving the Ethics Committee Approval of the same institute, numbered KAEK/2022.04.88. Before the study, we obtained informed consent from all the participants included in our study. We complied with the Declaration of Helsinki at all stages of the study. We compared the study groups' demographic information, hormonal parameters, ovarian volumes, and antral follicle numbers. We performed an independent t-test to compare group means. We used SPSS for Windows 24.0 (IBM Corp., Armonk, NY, USA) for the analyses. We considered the *p*-value lower than 0.05 to be statistically significant.**

**RESULTS: AMH values were 2.66±1.76 pmol/L in the control group and 1.61±0.86 pmol/L in the patient group. The total number of antral follicles was 10.25±2.13 (n) in the control group and 9.26±2.97 (n) in the study group. Ovarian volume was 11.57±1.37 ml in the control group and 10.63±1.96 ml in the study group. These results were statistically significantly different. We detected one premature ovarian failure (POI) in the study group. Although there was only one case, this difference between the groups was statistically significant.**

**CONCLUSIONS: Our study has proven that the ovaries of women of reproductive age suffering from any disease with an autoimmune etiology are affected by this autoimmune process. Therefore, ovarian reserves should be evaluated in all fertile women with autoimmune diseases. Due to the evaluation, appropriate treatment and follow-up plans should be made in patients with infertility or premature ovarian failure (POF) risk.**

*Key Words:*
Vitiligo, Ovarian reserve, Autoimmune disease.

## Introduction

Vitiligo is the most common depigmenting skin disease, with an estimated prevalence of 0.5-2% worldwide, regardless of gender[1,2]. Genetics, autoimmune responses, oxidative stress, formation of inflammatory mediators, and melanocyte separation mechanisms play a role in the formation of vitiligo[3,4]. Both immune system pathways play an active role in the etiology[5-7]. Molecules released from melanocytes and possibly keratinocytes induce innate immunity by exogenous or endogenous pathways and lead to melanocyte destruction[8,9]. In in the literature[10], it has been proven that antibodies against melanocyte surface antigens destroy melanocytes by complement-mediated lysis.

In many autoimmune disorders, one of the organs damaged by the immune attacks are the ovaries, and as a result, the reserves of the ovaries decrease[11]. Antral follicle count (AFC) and hormone levels are used to understand ovarian reserve. In the last decade, the anti-mullerian hormone (AMH) has been widely used to assess ovarian reserve. When researchers investigated all aspects of the ovarian reserve of this hormone in detail, they discovered that AMH measures ovarian reserve quite reliably[12]. Antimullerian hormone (AMH) is released from granulosa cells in preantral follicles and provides hormonal balance in the ovaries by preventing primordial follicles from collecting[13]. Recent studies[14,15] have shown that women suffering from an autoimmune disease have lower serum AMH levels. There is no data in the literature on whether vitiligo disease affects the ovarian reserves of women with vitiligo. For this reason, we aimed to compare ovarian capacity in women suffering from reproductive age with vitiligo and compare them with healthy women in the control group.


*Corresponding Author:* Ömer Ünal, MD; e-mail: dr.omer-unal@hotmail.com

## Patients and Methods

### Patients

We designed our study as a case-control study. Participants consisted of 71 people, 27 of whom were vitiligo patients. Patient group Vitiligo diagnosis consists of cases that have been proven both clinically and pathologically by dermatologists who worked in our same institute. We randomly selected the control group participants from the volunteers who came to the routine gynecological examination. The participants included in the study were 18-40 years old. We conducted the study between June 2022 and November 2022 at SBU Istanbul Kanuni Sultan Süleyman Training and Research Hospital, a tertiary hospital. We carried out the study after receiving the Ethics Committee Approval of the same institute, numbered KAEK/2022.04.88. Prior to the study, we obtained informed consent from all participants included. We complied with the Declaration of Helsinki at all stages of the study.

### Methods

We took detailed anamnesis of the participants and examined their health records. Demographic characteristics were age, body mass index (BMI), duration of vitiligo disease, smoking, gravida, and parity. On the third day of the participants' menstrual cycle, at 9:00 am, 3 cc of venous blood was taken from the antecubital region and put into a lithium-heparin tube. Follicle stimulating hormone (FSH), luteinizing hormone (LH), thyroid stimulating hormone (TSH), estradiol (E2), and antimullerian hormone (AMH) values were measured fully automatically. An electrochemiluminescence test (Roche Diagnostics, Basel, Switzerland) was used for measurements. All measurements were performed on the same device in the biochemistry laboratories of the same institute. In the same session, we measured the antral follicle count (AFC) and the total volume of the ovaries using the same transvaginal ultrasound (TVUSG) (8.5 MHz transvaginal transducer ATL 5000 HDI, Philips, Amsterdam, The Netherlands) device.

### Inclusion Criteria

While forming the patient group, we included cases diagnosed with vitiligo, aged 18-40 years, without any other autoimmune disease. While forming the control group, we included volunteers in the same age range, who did not have any other autoimmune disease, and whose menses were regular.

### Exclusion Criteria

We listed the exclusion criteria from the study as follows; having another autoimmune disease, being younger than 18 and older than 40, being pregnant, having polycystic ovary syndrome (PCOS), undergoing previous surgery on the uterus and ovaries, receiving chemotherapy or radiotherapy due to other oncological reasons, benefiting from assisted reproductive techniques, using hormone-containing drugs (Figure 1).

### Statistical Analysis

We used SPSS for Windows 24.0 (IBM Corp., Armonk, NY, USA) for the analyses. While comparing the data we obtained in our study with the independent *t*-test, we applied Pearson's correlation analysis to reveal the relationship between the duration of vitiligo disease and the parameters that help us determine ovarian reserve. We presented the data as mean, standard deviation, and ratio and considered them statistically significant when the *p*-value was lower than 0.05.

## Results

AMH values, one of the main features of our study, were 2.66±1.76 pmol/L in the control group and 1.61±0.86 pmol/L in the vitiligo patient group, and this result was statistically significant. We determined the total number of antral follicles used to determine ovarian reserves as 10.25±2.13 (n) in the control group and 9.26±2.97 (n) in the study group, and this result was statistically significant. Ovarian volume, which sheds light on ovarian reserves, was 11.57±1.37 ml in the control group and 10.63±1.96 ml in the study group. These results were statistically significantly different. We detected one premature ovarian failure (POI) in the study group. Although there was only one case, this difference between the groups was statistically significant. When we compared the demographic characteristics of the participants included in our study, we did not find a statistical difference (Table I). As can be seen in the same table, some hormonal results did not make a statistical difference.

When we performed a Pearson's correlation analysis between the duration of the disease and the parameters related to the ovarian reserve in cases suffering from vitiligo disease (Table II), it showed a negative correlation with the duration of disease exposure and AMH, prolactin, and ovarian volume. This correlation was statistical-

**Table I.** Comparison of demographic, hormonal, and ultrasonographic results.

| | Vitiligo group n=27 | | Control group n=44 | | |
|---|---|---|---|---|---|
| | Mean | Standard deviation | Mean | Standard deviation | *p*-value |
| Age (year) | 31.44 | 6.67 | 31.64 | 5.91 | 0.588 |
| Gravia | 1.20 | 1.59 | 1.85 | 1.35 | 0.273 |
| Parite | 0.93 | 1.19 | 1.59 | 1.05 | 0.306 |
| BMI (kg/m2) | 26.49 | 3.44 | 24.91 | 4.12 | 0.162 |
| Smoking | 18.52% | - | 22.73% | - | 0.399 |
| Chronic disease (HT, DM, Dyslipidemia) | 3.70% | - | 6.82% | - | 0.755 |
| Duration of vitiligo (year) | 7.15 | 3.22 | - | - | - |
| POF (Premature ovarian failure) | 3.70% | - | 0% | - | 0.01* |
| AMH (pmol/L) | 1.61 | 0.86 | 2.66 | 1.76 | 0.0001* |
| FSH (IU/L) | 7.04 | 5.13 | 6.47 | 2.25 | 0.178 |
| LH (IU/L) | 8.08 | 2.44 | 6.02 | 2.08 | 0.723 |
| Prolactin (ng/mL) | 12.55 | 6.96 | 15.77 | 8.05 | 0.299 |
| Total testosterone (ng/dl) | 0.23 | 0.11 | 0.28 | 0.15 | 0.082 |
| E2 (pmol/L) | 43.22 | 19.13 | 62.78 | 54.60 | 0.167 |
| TSH (mIU/mL) | 2.02 | 1.03 | 2.34 | 1.35 | 0.990 |
| DHEAS (ng/ ml) | 198.92 | 98.85 | 244.88 | 114.53 | 0.592 |
| AFC | 9.26 | 2.97 | 10.25 | 2.13 | 0.003* |
| Total ovarian volume (ml) | 10.63 | 1.96 | 11.57 | 1.37 | 0.001* |
| hsCRP (mg/L) | 0.5 (0.35-1.45) | 10.8 (4.8-19.0) | <0.001 | | |
| SAA1 (mg/L) | 3.76 (2.69-7.91) | 8.82 (5.99-30.52) | 0.014 | | |
| sPD-L1 (ng/L) | 89.9 (51.8-107.1) | 297.5 (117.7 -545.9) | <0.001 | | |

$p<0.05$, independent *t*-test, *: statistically significant.

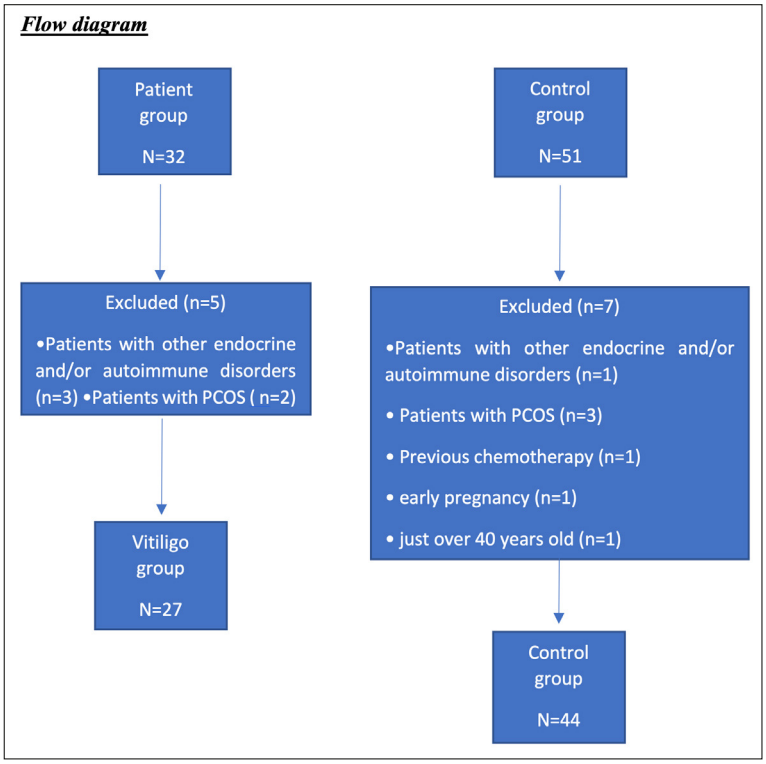


**Figure 1.** Flowchart of the study population.

**Table II.** Pearson's correlation analysis of the duration of vitiligo disease and hormonal and ultrasonographic data.

| | | AMH | FSH | LH | Prolactin | Total Testosterone | E2 | TSH | DHEAS | AFC | Ovarian Volume | POF |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Duration of vitiligo | r | -0.317** | 0.025 | 0.238* | -0.236* | -0.121 | -0.187 | -0.168 | -0.095 | -0.092 | -0.306** | 0.249* |
| | *p* | 0.007 | 0.837 | 0.045 | 0.047 | 0.317 | 0.119 | 0.162 | 0.431 | 0.447 | 0.009 | 0.036 |

*$p<0.05$, **: $p<0.01$ Pearson's correlation analysis.

ly significant ($r$=-0.317**, $p$=0.007), ($r$=-0.236*, $p$=0.047), ($r$=-0.306**, $p$=0.009). Again, there was a statistically significant positive correlation between the duration of vitiligo disease and LH and POF rates ($r$=0.238*, $p$=0.045), ($r$=0.249*, $p$=0.036). We could not detect a relationship between the other parameters that determine the ovarian reserve and the duration of the disease.

## Discussion

Autoimmune diseases generally use the same cascade when they occur and mimic each other at this stage[16]. Someone with a single autoimmune disorder at baseline has a 25% chance of developing another disease[16]. The rate of ovarian failure in reproductive women suffering from an autoimmune disease is 4-30%[17]. Conway et al[18] examined 135 cases with proven POF, 13 (10%) revealed an overt autoimmune disease. In another study, Alper and Garner[19,20] found that 13 (39%) of 33 women suffering from POF had an autoimmune disease. In the study by Alper and Garner[19,20] eleven patients had autoimmune thyroid disease, one had Addison's disease, and one had vitiligo. In light of this information, we would compare the parameters that measured the ovarian reserves of the vitiligo cases and the control group. We also examined the relationship between vitiligo duration and these parameters.

The predictive values of ovarian reserve tests have often been considered, but neither is ideal alone[21]. Ovarian assessment with AMH, FSH, LH, E2, ovarian volume, and AFC is the method of choice for disease-affected ovarian reserve[12,22]. POF status is defined as early depletion/arrested folliculogenesis of ovarian follicles before age 40 with elevated FSH levels (>40 IU/L) and hypoestrogenism[23]. POF is associated with autoimmune diseases and endocrinopathies in 20-30% of cases[12]. Viruses, bacteria, or ovarian cell antigens can initiate the autoimmune process with destruction in ovarian tissues. An autoimmune effect has been demonstrated in approximately one-third of POI cases[24]. Coulam and Ryan[25] found antibodies against ovarian tissue in 19.2% of POI cases. Vitiligo is found in 1% of POI cases[12]. Indeed, in our study, we found a statistically significant 3.7% POI in the study group with vitiligo. AMH is a reliable hormone that indicates ovarian antral follicle well-being[12,26]. Recent studies[14,27,28] prove that women suffering from an autoimmune disease have low AMH values. In this study, we also found low AMH values in patients with vitiligo, which aligns with the literature. The AFC used to evaluate ovarian reserve has decreased with age and correlates with other markers[29]. However, recent studies[14,27,28] have shown that AFC is reduced in some autoimmune diseases. This study found low AFC in vitiligo cases, which supports the literature. One of the parameters used to determine ovarian reserve is ovarian volume[16,17]. When we look at the literature, it is understood that the ovarian volume decreases in cases suffering from autoimmune disease[30]. In our study, in parallel with the literature, ovarian volume decreases in cases with vitiligo. Although we could not find any study dealing with vitiligo and ovarian reserve when we reviewed the literature, we see that in recent literature, a negative correlation was found between disease exposure time and AMH and ovarian volume in patients suffering from an autoimmune disease[30]. In the literature search, we did not find a study that would explain the positive correlation between disease exposure time and prolactin and LH, as in our study. However, more comprehensive studies are needed to explain such a situation.

## Conclusions

What we found in our study is that vitiligo, an autoimmune disease, affects ovarian reserve negatively. Therefore, as soon as vitiligo and other autoimmune diseases are diagnosed, the ovarian reserve should be evaluated in all reproductive women and followed routinely. If the ovarian reserve is affected, appropriate treatment and follow-up plans should be established.

### Conflict of Interest
The Authors declare that they have no conflict of interests.

### Acknowledgments
The authors are very grateful to the reviewers and editors who evaluated the manuscript with interest and relevance.

### Funding
The authors received no financial assistance for this study.

### Authors' Contributions
Study concept and design: OU; data collection and drafting of the manuscript: OU and NT; review and final approval of the article: OU and NT.

### ORCID ID
Ömer Ünal: 0000-0001-7094-9025.

### Data Availability
All data related to this study are reproducible and transparent. All data is archived. It is not possible to present all the raw data in the article. Therefore, upon request, the data can be shared by the corresponding author.

### Ethics Approval
This study was conducted by the 2013 revision of the Declaration of Helsinki and was approved by the Ethics Committee of Istanbul Kanuni Sultan Süleyman Training and Research Hospital (KAEK 2022.04.88).

### Informed Consent
Written informed consent was obtained from each patient after a full oral and written explanation of the nature of the study, prior to enrollment in the study, and before any study-related activity. In addition, a copy was given to the participants and a copy was put in the archive.

## References

1) Alikhan A, Felsten LM, Daly M, PetronicRosic V. Vitiligo: a comprehensive overview Part I. Introduction, epidemiology, quality of life, diagnosis, differential diagnosis, associations, histopathology, etiology, and work-up. J Am Acad Dermatol 2011; 65: 473-491.
2) Krüger C, Schallreuter KU. A review of the worldwide prevalence of vitiligo in children/adolescents and adults. Int J Dermatol 2012; 51: 1206-1212.
3) Ezzedine K, Lim HW, Suzuki T, Katayama I, Hamzavi I, Lan CCE, Goh BK, Anbar T, de Castro CS, Lee AY, Parsad D, van Geel N, Le Poole IC, Oiso N, Benzekri L, Spritz R, Gauthier Y, Hann SK, Picardo M, Taieb A. Vitiligo Global Issue Consensus Conference Panelists. Revised classification/nomenclature of vitiligo and related issues: the Vitiligo Global Issues Consensus Conference. Pigment Cell Melanoma Res 2012; 25: E1-E13.
4) Rodrigues M, Ezzedine K, Hamzavi I, Pandya AG, Harris JE; Vitiligo Working Group. New discoveries in the pathogenesis and classification of vitiligo. J Am Acad Dermatol 2017; 77: 1-13.
5) Ezzedine K, Eleftheriadou V, Whitton M, van Geel N. Vitiligo. Lancet 2015; 386: 74-84.
6) Sandoval-Cruz M, García-Carrasco M, Sánchez-Porras R, Mendoza-Pinto C, Jiménez-Hernández M, Munguía-Realpozo P, Ruiz-Argüelles A. Immunopathogenesis of vitiligo. Autoimmun Rev 2011; 10: 762-765.
7) Richmond JM, Frisoli ML, Harris JE. Innate immune mechanisms in vitiligo: danger from within. Curr Opin Immunol 2013; 25: 676-682.
8) van den Boorn JG, Picavet DI, van Swieten PF, van Veen HA, Konijnenberg D, van Veelen PA, van Capel T, de Jong EC, Reits EA, Drijfhout JW, Bos JD, Melief CJM, Luiten RM. Skin-depigmenting agent monobenzone induces potent T-cell autoimmunity toward pigmented cells by tyrosinase haptenation and melanosome autophagy. J Invest Dermatol 2011; 131: 1240-1251.
9) Yu R, Broady R, Huang Y, Wang Y, Yu J, Gao M, Levings M, Wei S, Zhang S, Xu A, Su M, Dutz J, Zhang X, Zhou Y. Transcriptome analysis reveals markers of aberrantly activated innate immunity in vitiligo lesional and non-lesional skin. PLoS One 2012; 7: e51040.
10) Ongenae K, van Geel N, Naeyaert JM. Evidence for an autoimmune pathogenesis of vitiligo. Pigment Cell Res 2003; 16: 90-100.
11) Petrikova J, Lazurova I. Ovarian failure and polycystic ovary syndrome. Autoimmun Rev 2012; 11: A471-A478.
12) Broer SL, Broekmans FJ, Laven JS, Fauser BC. Anti-Müllerian hormone: ovarian reserve testing and its potential clinical implications. Hum Reprod Update 2014; 20: 688-701.
13) Monniaux D, Clément F, Dalbiès-Tran R, Estienne A, Fabre S, Mansanet C, Monget P. The ovarian reserve of primordial follicles and the dynamic reserve of antral growing follicles: what is the link? Biol Reprod 2014; 90: 85.
14) Lawrenz B, Henes JC, Henes M, Neunhoeffer E, Schmalzing M, Fehm T, Kïtter I. Impact of systemic lupus erythematosus on ovarian reserve in premenopausal women: evaluation by using anti-Muellerian hormone. Lupus 2011; 20: 1193-1197.

15) Şenateş E, Çolak Y, Erdem ED, Yeşil A, Coşkunpınar E, Şahin Ö, Altunöz ME, Tuncer I, Övünç AOK. Serum anti-Mullerian hormone levels are lower in reproductive-age women with Crohn's disease compared to healthy control women. J Crohns Colitis 2013; 7: e29-e34.
16) Harpreet S, Deepak J, Kiran B. Multiple autoimmune syndrome with celiac disease. Reumatologia 2016; 201654: 326-329.
17) Karakus S, Sahin A, Durmaz Y, Aydin H, Yildiz C, Akkar O, Dogan M, Cengiz A, Cetin M, Cetin A. Evaluation of ovarian reserve using anti-müllerian hormone and antral follicle count in Sjögren's syndrome: Preliminary study. J Obstet Gynaecol Res 2017; 43: 303-307.
18) Conway GS, Kaltsas G, Patel A, Davies MC, Jacobs HS. Characterization of idiopathic premature ovarian failure. Fertil Steril 1996; 65: 337-341.
19) Alper MM, Garner PR, Seibel MM. Premature ovarian failure. Current concepts. J Reprod Med 1986; 31: 699-708.
20) Alper MM, Garner PR. Premature ovarian failure: its relationship to autoimmune disease. Obstet Gynecol 1985; 66: 27-30.
21) Jirge PR. Ovarian reserve tests. J Hum Reprod Sci 2011; 4: 108e13.
22) Oner G, Muderris II. Assessment of ovarian reserve based on hormonal parameters, ovarian volume, and antral follicle count in women with familial Mediterranean fever. Eur J Obstet Gynecol Reprod Biol 2013; 170: 449e51.
23) Beck-Peccoz P, Persani L. Premature ovarian failure. Orphanet J Rare Dis 2006; 1: 9.
24) Wu JJ, Nguyen TU, Poon KY, Herrinton LJ. The association of psoriasis with autoimmune diseases. J Am Acad Dermatol 2012; 67: 924e30.
25) Fénichel P, Sosset C, Barbarino-Monnier P, Gobert B, Hiéronimus S, Béné MC, Harter M. Prevalence, specificity and significance of antiovarian antibodies during spontaneous premature ovarian failure. Hum Reproad 1997; 12: 2623-2628.
26) Coulam CB, Ryan RJ. Premature menopause.I. Etiology. Am J Obstet Gynecol 1979; 133: 639-643.
27) Medicine PCotASfR. Testing and interpreting measures of ovarian reserve: a committee opinion. Fertil Steril 2015; 103: e9-e17.
28) Ulug P, Oner G, Kasap B, Akbas EM, Ozcicek F. Evaluation of ovarian reserve tests in women with systemic lupus erythematosus. Am J Reprod Immunol 2014; 72: 85e8.
29) Yamakami LYS, Serafini PC, de Araujo DB, Bonfá E, Leon EP, Baracat EC, Silva CA. Ovarian reserve in women with primary antiphospholipid syndrome. Lupus 2014; 23: 862e7
30) Haadsma ML, Bukman A, Groen H, Roeloffzen EMA, Groenewoud ER, Heineman MJ, Hoek A. The number of small antral follicles (2-6 mm) determines the outcome of endocrine ovarian reserve tests in a subfertile population. Hum Reprod 2007; 22: 1925e31.
31) Aydogan Mathyk B, Aslan Cetin B, Bilici S, Fasse J, Avci P. Evaluation of ovarian reserve in women with psoriasis. Gynecol Endocrinol 2019; 35: 608-611.