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Circulating Androgen Levels in Women with Premature Ovarian Insufficiency

Prematür Over Yetmezliği Tanısı Alan Kadınlarda Serum Androjen Seviyeleri

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ABSTRACT

Objective: The objective of our study was to assess the androgen status in women with premature ovarian insufficiency (POI) compared to age-matched regularly menstruating women. **Material and Methods:** Sixty-two women with POI and 62 healthy women with regular menstrual cycles as the control group participated in this case control study. The information about their clinical characteristics were collected. Serum hormone parameters included total testosterone, sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS), dehydroepiandrosterone (DHEA), and androstenedione (AS). Levels of follicle stimulating hormone (FSH), estradiol and AMH were also measured. Additionally, the free androgen index (FAI), and bioavailable testosterone were calculated. **Results:** The levels of total testosterone, calculated androgen indices (bioavailable testosterone, FAI), SHBG and DHEA did not differ between POI group and the control group. The levels of DHEAS and AS were significantly lower in POI group compared with the controls (p=0.002; p=0.036, respectively). In our study, only 15 of the 62 women with POI (24%) used HRT. DHEAS levels were significantly higher in the control group compared to the women with POI who did or did not use HRT (p=0.002). BMI correlated positively with FAI (r= 0.318, p< 0.001) and with bioavailable testosterone (r= 0.241, p= 0.008). An inverse correlation was found between age and DHEAS levels (r= -0.209, p= 0.002). **Conclusion:** Our findings indicate that the androgen profile in women with POI is similar to those observed in healthy controls with the exception of serum DHEAS levels. This study showed that androgen decline seen in POI may be primarily related to an adrenal defect.

Keywords: Premature ovarian insufficiency, androgen, testosterone, DHEAS

ÖZET

Amaç: Bu çalışmada prematür over yetmezliği (POY) tanısı alan kadınlarla aynı yaşta düzenli adet gören kadınlardaki serum androjen seviyelerinin karşılaştırılması amaçlanmıştır. **Gereç ve Yöntemler:** POY tanısı almış 62 hasta ve düzenli adet siklusu olan 62 kadından oluşan sağlıklı kontrol grubu vaka kontrol çalışmasına dahil edildi. Hastaların demografik özellikleri ve klinik bilgileri sorgulandı. Serum hormon parametreleri arasında total testosteron, seks hormon bağlayıcı globulin (SHBG), dehidroepiandrosteron sülfat (DHEAS), dehidroepiandrosteron (DHEA) ve androstenedion (AS), folikül uyarıcı hormon (FSH), estradiol ve antimüllerian hormon (AMH) seviyeleri ölçüldü. Ek olarak serbest androjen indeksi (FAI) ve biyolojik olarak kullanılabilir (bioavailable) testosteron seviyeleri hesaplandı. **Bulgular:** POY grubu ile kontrol grubu arasında total testosteron, hesaplanan androjen indeksleri (bioavailable testosteron, FAI), SHBG ve DHEA seviyeleri arasında fark bulunmazken DHEAS ve AS konsantrasyonu, POY grubunda kontrol grubuna göre anlamlı olarak daha düşük olarak saptandı (sırasıyla p=0,002; p=0,036). Çalışmamızda POY tanısı alan 62 kadından sadece 15'i (%24) HRT kullanmıştır. DHEAS konsantrasyonu kontrol grubunda, POY'lu kadınlara (HRT kullanan veya kullanmayan) kıyasla anlamlı olarak daha yüksekti (p=0.002). BMI, FAI (r= 0.318, p< 0.001) ve bioavailable testosteron (r= 0.241, p= 0.008) ile pozitif korelasyon gösterdi. Yaş ile DHEAS düzeyleri arasında ters yönde korelasyon saptandı (r= -0.209, p= 0.002). **Sonuç:** Bulgularımız POY grubunda serum androjen profilinin DHEAS seviyeleri haricinde sağlıklı kontrol grubuyla benzer olduğunu göstermektedir. Bu çalışma POY'da görülen androjen düşüklüğü primer olarak bir adrenal defekte bağlı olabileceğini göstermiştir.

Anahtar Kelimeler: Prematür over yetmezliği, androjen, testosteron, DHEAS

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Premature ovarian insufficiency (POI) is defined by amenorrhea for at least 4 months with repeatedly elevated FSH concentrations in women younger than 40 years of age.[1] Due to atrophy of the ovarian cortex, women with POI suffer from loss of ovarian androgens in addition to estrogen deficiency.[2] Lack of androgens may lead to symptoms such as unexplained fatigue, cognitive dysfunction, decreased libido and sexual dysfunction and.[3-6]

In premenopausal women, about 50% of the testosterone secretion is derived from the ovary and the adrenal gland, and the remaining 50% is produced from the peripheral conversion of androgen precursors.[7] The adrenals have been considered the major source of dehydroepiandrosterone sulfate (DHEAS) and androstenedione (AS).[8] Androstenedione is produced by the adrenal gland (50%) as well as the ovarian stroma (50%) whereas DHEAS is exclusively produced by the adrenal glands and is converted to dehydroepiandrosterone (DHEA) by steroid sulphatase. DHEA is secreted in both the ovaries (20%) and the adrenal glands (50%), with 30% being derived from circulating DHEAS.[7,9] It was reported higher levels of dehydroepiandrosterone sulfate in POI versus postmenopausal controls, but no significant change in testosterone and androstenedione levels was observed between POI women and the postmenopausal group.[10]

It is still uncertain whether POI is a cause of clinically significant androgen- deficiency or not.[11-13] Some studies have demonstrated that there is a continuing decline in serum androgen levels with age and that there is no independent influence of menopause on a further reduction.[8,14] If there is indeed a remarkable decline in serum androgen levels, androgen replacement therapy might be advocated for augmenting the standard estrogen-based hormone therapy for women with POI, while it needs to be confirmed by further investigations.[15]

The objective of our cross-sectional study was to assess the androgen status in women with spontaneous POI compared with regularly cycling women in the same age range.

MATERIALS AND METHODS

The study was a prospectively designed case control study. The androgen profiles of 62 consecutive POI women aged 20-42 years who were referred to the outpatient clinic of Obstetrics and Gynecology, Bezmialem Vakif University, Istanbul, Turkey between January 2020 and January 2021, were included in this study. The time of diagnosis was before the age of 40 in these women was defined by at least four months of oligomenorrhea/amenorrhea and by follicle-stimulating hormone (FSH) levels of ≥25 mIU/ml measured on at least two occasions with a month apart.[1] Exclusion criteria for women with POI were history of hysterectomy and/or oophorectomy, chemotherapy and/or pelvic radiotherapy, and chronic illnesses. None of the subjects had any clinical signs or symptoms of hyperandrogenism. Patients with POI typically presented with menstrual disturbance (amenorrhea or oligomenorrhea), infertility, symptoms of estrogen deficiency such as vasomotor instability (hot flushes, night sweats), mood disturbances, vaginal dryness and sleep disorders.

The control group consisted of 62 regularly menstruating age-matched women with cycles of 24 to 35 days who did not take any form of hormonal therapy/contraception for at least 3 months prior to the study enrollment. Exclusion criteria for the control group included lack of any signs of clinical or biochemical hyperandrogenism or female reproductive dysfunction.

Demographic, anthropometric and clinical characteristics were collected for all women, including age, weight, height, educational level (years), marital and working status (housewife/unemployed, working), number of children, number of miscarriages, smoking status (yes or no), physical activity (yes or no), and use of hormone replacement therapy (HRT). Body mass index (BMI) was calculated as kg/m^2. Marital status was categorized into married or unmarried (single, divorced, widowed, etc.). Physically active was defined as subjects carrying out more than 30 minutes of physical activity at least three times per week.[6,16]

Serum levels of FSH, estradiol (E2), anti-Müllerian hormone (AMH), total testosterone, sex hormone-binding globulin (SHBG), DHEAS, AS, DHEA and albumin were evaluated in all women. After an overnight fast, blood samples were drawn between 8 and 11 am. Blood samples of the controls were drawn

between the 2nd and 5th days of their menstrual cycle. In women with POI who were using HRT, samples were obtained during the days on which the combined pills (eg, estrogen and progesterone) were taken. On the other hand, the samples were obtained on any day in women with POI not receiving HRT.

Plasma FSH and DHEAS concentrations were measured by a direct chemiluminescence immunoassay, E2 and total T concentrations were determined by a competitive chemiluminescent immunoassay, and albumin concentrations were analyzed by photometric assays (ADVIA Centaur, Siemens Healthcare Diagnostics). Androstenedione and DHEA were measured using liquid chromatography-tandem mass spectrometry with an Agilent 6460 triple quadrupole mass spectrometer (Agilent Technologies, Germany). SHBG was determined using a sandwich immunoassay (Roche/Hitachi Cobas c system). AMH levels were measured using electrochemiluminescence immunoassays. Free androgen index (FAI) was calculated as total testosterone/SHBG×100.[17] Bioavailable testosterone was calculated by an online calculator on http://www.issam.ch/freetesto.htm.[18]

The study was approved by the ethical board of Bezmialem University (number: 02/29), and written informed consent was obtained from all participants. Study was conducted according to the declaration of Helsinki.

STATISTICAL ANALYSIS

Statistical analysis was performed after normality testing (histogram analysis and/or Kolmogorov-Smirnov testing) using IBM SPSS, version 21 (IBM Inc., Armonk, NY). The student's t-test was used for comparisons of normally distributed variables, the Mann-Whitney U-test was used for non-parametric variables, χ^2 test, and Fisher's exact tests were used to compare categorical variables. The Spearman or Pearson correlation was applied in cases where the normality of the data was questionable. P <0.05 was considered statistically significant.

RESULTS

The age of women with POI was 37.4±4.1 years, and BMI was 25.8±4.2. The age of the control women was 36.2±3.4 years and their BMI was 26.1±4.3. Table 1 demonstrates the demographic and clinical characteristics of the study and control groups. The women with POI and the controls showed no differences in the mean age, body mass index, educational level, marital and working status and smoking. Similarly, there was no difference between the groups regarding the number of children, the number of miscarriages, or desire to have more children.

Table 2 shows the hormone profiles of women with POI and the control group. As expected, women with POI had higher levels of serum FSH (p<0.0001), lower levels of E2 (p<0.0001) and AMH (p<0.0001) compared to the control women. The levels of total testosterone, calculated androgen indices (bioavailable testosterone, FAI), SHBG and DHEA did not differ between the POI group and the control group, while the levels of DHEAS, and AS were significantly lower in the POI group compared with the controls (p=0.002; p=0.036, respectively).

TABLE 1: Sociodemographic characteristics of women with POI and control women

	POI group (n=62)	Control group (n=62)	p
Age[a]	37.4 ± 4.1	36.2 ± 3.4	0.06
BMI, (kg/m^2)[b]	25.8 ± 4.2	26.1 ± 4.3	0.7
Education level, n(%)[c]			
0-5 years	25 (40.3)	20 (30.8)	0.6
6-8 years	20 (32.3)	17 (26.2)	
>8	17 (27.4)	28 (43.1)	
Marital status, n(%)[c]			
Married	51 (82.3)	52 (83.9)	0.8
Single/Divorced/Widowed	11 (17.7)	10 (16.1)	
Work status, n(%)[c]			
Working	28 (45.2)	32 (51.6)	0.5
Housewife/unemployed	34 (54.8)	30 (48.4)	
Number of children[a]	1.3 ± 1.2	0.9 ± 1.1	0.1
Number of miscarriages[a]	0.3 ± 0.6	0.2 ± 0.4	0.5
Smoker, n(%)[c]	20 (32.3)	12 (19.4)	0.1
Physical active, n(%)[c]	17 (27.4)	20 (32.3)	0.5

Data are expressed as mean ± standard deviation or n (%).
POI, premature ovarian insufficiency; BMI, body mass index.
[a]Mann-Whitney test.
[b]Student's t-test.
[c]Chi-square test.

TABLE 2: Hormonal parameters of women with POI and control women.

	POI group (n=62)	Control group (n=62)	p
FSH (mIU/ml)	49.05±29.76	6.79±2.72	<0.0001
E2 (pg/ml)	22.26±16.82	55.06±26.19	<0.0001
AMH (ng/ml)	0.07±0.22	1.29±1.23	<
Total T (ng/ml)	0.25±0.12	0.23±0.11	0.6
Androstenedione (ng/ml)	0.59±0.3	0.7±0.27	0.036
DHEA(ng/dl)	401.06±210.87	426.85±222.4	0.5
DHEAS (µg/dl)	168.20±84.37	233.64±139.78	0.002
SHBG (nmol/l)	67.65±48.53	62.70±27.47	0.5
FAI	0.52±0.33	0.53±0.29	0.9
Bioavailable testosterone (ng/ml)	0.08±0.04	0.08±0.03	0.8

Data are shown as mean ± standard deviation.
FSH, follicle-stimulating hormone; E2, estradiol; AMH, anti-Müllerian hormone; T, testosterone; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; SHBG, sex hormone-binding globulin; FAI, free androgen index.

Figure 1, Figure 2 show the androgen levels of women with POI and the controls. In our study, only 15 of the 62 women with POI (24%) used HRT. DHEAS levels were significantly higher in the control group compared to the women with POI who did or did not use HRT. Total testosterone, bioavailable testosterone, FAI, SHBG, AS and DHEA levels were not different between the control group and the women with POI whether or not using HRT.

Correlational analysis was performed in the whole cohort and BMI correlated positively with FAI (r=0.318, p<0.001), and with bioavailable testosterone (r=0.241, p=0.008) while BMI showed an inverse correlation with SHBG levels (*r*=-0.355; p<0.001). An inverse correlation was also found between the age and DHEAS levels (r=-0.209, p=0.002).

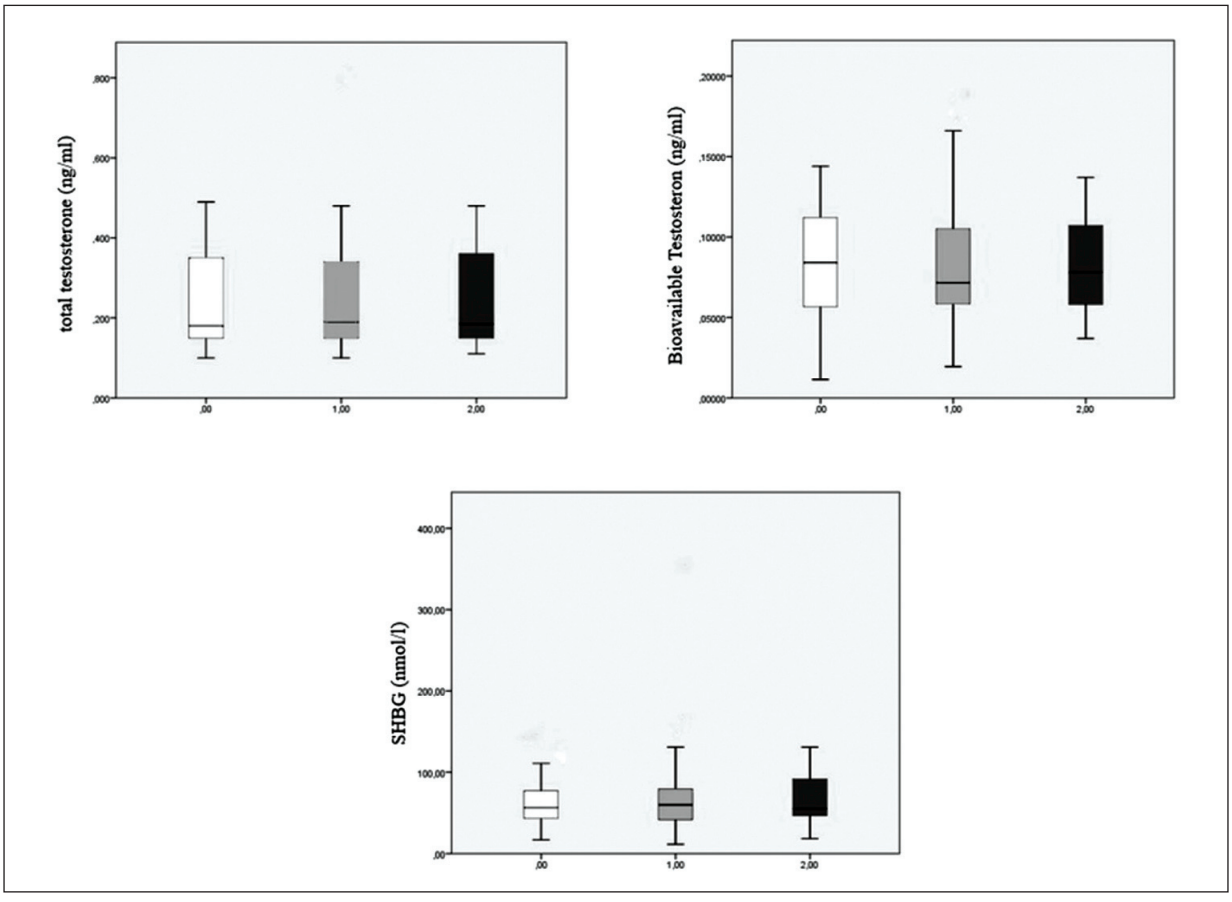

FIGURE 1: Total testosterone, bioavailable testosterone, SHBG levels of women with POI who were using HRT (gray boxes), not using HRT (black boxes), and the controls (white boxes). SHBG: Sex hormone-binding globulin.

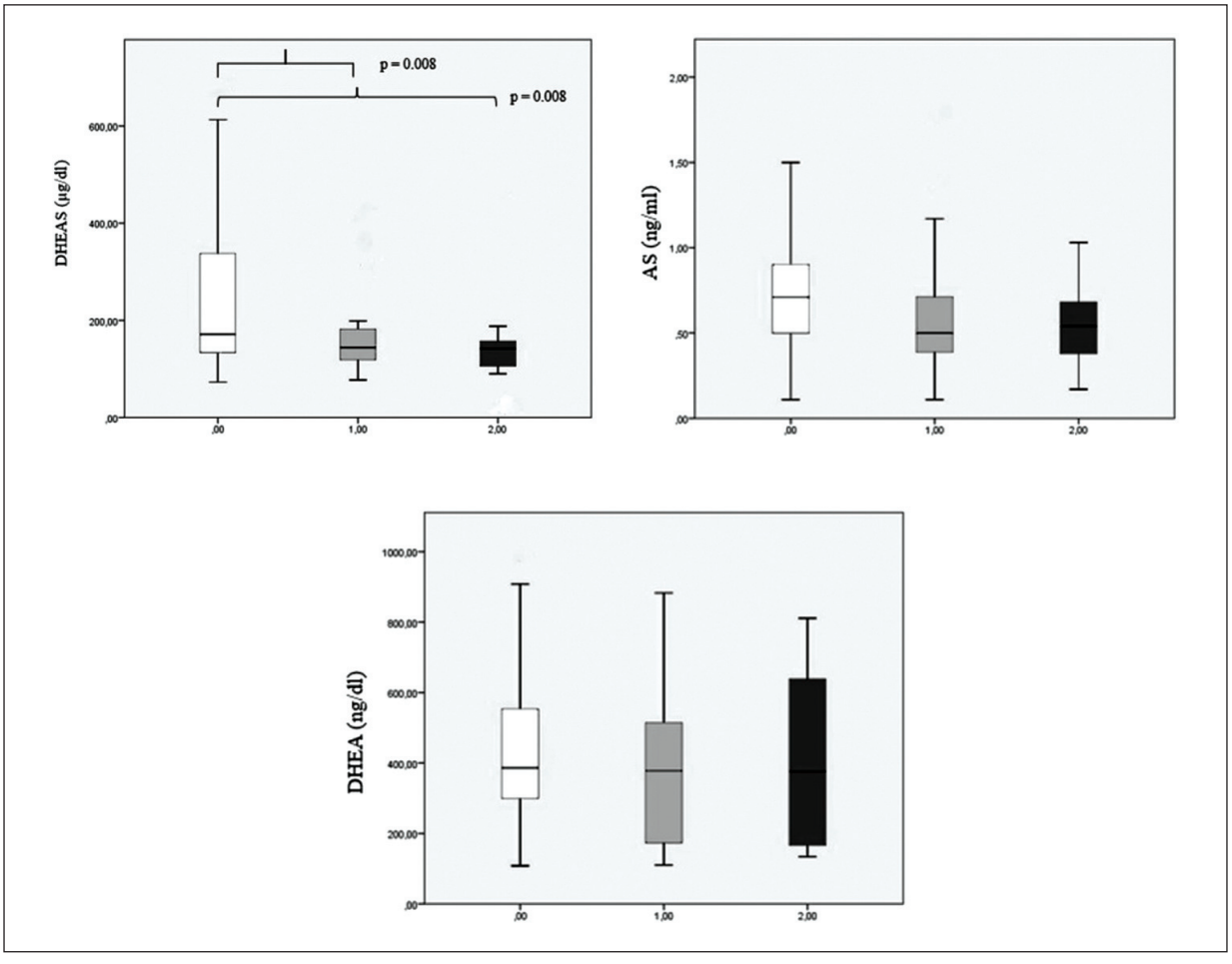

FIGURE 2: DHEAS, AS, DHEA levels of women with POI who were using HRT (gray boxes), not using HRT (black boxes), and the controls (white boxes). P levels of significant statistical difference were indicated for DHEAS. DHEAS: dehydroepiandrosterone sulfate, AS: Androstenedione, DHEA: Dehydroepiandrosterone.

DISCUSSION

Although majority of POI cases are idiopathic and etiology is poorly understood, genetic factors, autoimmune disorders and iatrogenic causes, infectious agents, toxins are suggested to be related with its pathogenesis.[19,20] Complete loss of androgen biosynthesis may occur in POI combined with other androgen depleting diseases such as autoimmune adrenal failure and long-term glucocorticosteroid therapy.[21,22]

Studies that compare androgen levels in women with spontaneous POI and healthy women are sparse in literature. In this study, we found no significant difference in the total testosterone levels or calculated androgen indices between the women with POI and the control group. Our findings are in agreement with the previous studies, which found similar levels of testosterone in women with POI compared to regularly menstruating women.[3,14] Although the ovarian contribution to androgen production in postmenopausal women is still controversial, it has been suggested that natural menopause is not a cause of abrupt decline in testosterone levels possibly secondary to the increase of LH-induced intra-ovarian theca cell androgen production.[23] However, a previous meta-analysis reported that the levels of testosterone were lower in the group with POI compared to those in the fertile control group and proposed that the decline in circulating testosterone may occur as a result of diminished ovarian androgen production.[24] Although we did not report any difference in bioavailable testosterone levels among women with POI depending on the use of HRT, van der Stege et al. reported lower bioavailable testosterone levels in

women with POI who used HT and suggested that using HRT is associated with an increase in SHBG concentrations, which results in decreased plasma concentrations of bioavailable testosterone.[2] We have also identified similar levels of SHBG in women with POI compared to controls, which is similar to the results obtained by Soman et al.[10] A recent review by Moulana reported that the modest increase in androgens in females was associated with increased pro-inflammatory cytokines and T lymphocytes, and therefore may contribute to development of hypertension.[25] Findings from another recent study found no relationship between circulating levels of sex hormones and brain aging in older women.[26]

Our results showed that the levels of DHEA-S in women with POI both using and not using HT were significantly lower than those in the control group, which is in line with the results obtained by Doldi et al. and Falsetti et al. who reported lower DHEAS levels in 25 and 40 women with POI, respectively, compared to control group.[27,28] Doldi et al. suggested that the low levels of DHEAS were related to the presence of organ-specific autoantibodies.[27] Existing data on DHEAS levels in women with POI are conflicting. Hartman et al. and Elias et al. observed that serum levels of DHEAS in women with POI were similar to those in the same number of controls.[3,13] More recently, Soman M et al. have also reported that serum DHEAS levels were lower in women with POI compared with regularly menstruating women.[10] Additionally, they noted that the serum DHEAS levels were still higher in POI women than that in postmenopausal women. It is stated that the significant reduction in DHEAS levels may also be a result of aging. In contrast, a previous study has reported a precipitous fall in DHEAS levels in women with POI, either spontaneous or surgically induced, and suggested that ovarian factors account for the decrease in DHEAS levels independent of age.[29] The fact that all androgen levels except for DHEA-S, which is primarily produced by adrenal glands, are the same in women with POI and the control group shows that the androgen decline in POI may be primarily due to an adrenal defect rather than menopause itself. Future studies are warranted to clarify the underlying reasons responsible for the observed decreased DHEAS levels in women with POI.

The correlation between age and DHEAS levels in our study reveals the significance of the effect of age on the adrenal production of DHEAS rather than the decreased number of theca cells as seen in diminished ovarian reserve (DOR).[30] Gleicher et al emphasize the importance of age and reported profoundly higher levels of DHEAS in older women with physiological DOR compared to POI, which they interpreted as a problem of adrenal conversion. Benetto et al. also demonstrated a negative correlation between age and DHEAS.[14] Furthermore, we observed a negative correlation between BMI and SHBG. Such a correlation has been reported before in pre-as well as postmenopausal women by Rannevik et al.[31]

Reduced levels of circulating androgens in women may create significant problems such as sexual dysfunction, decreased libido, diminished sense of well-being, changes in cognition and memory and dysphoric mood.[3-6,32] The clinical relevance of declining androgen levels in women is still an area of significant controversy. Evaluating androgen levels in women with POI may be beneficial as it has been suggested that androgen replacement in addition to estrogen-based therapies may be beneficial to improve several parameters of sexual function and well-being.[10,15,32]

STUDY LIMITATIONS

The present study was limited by the relatively small sample sizes and the lack of reliable data on duration of estrogen deficiency, because most of our subjects with POI were unable to report an accurate date of their last menstrual period.

CONCLUSION

The present study reveals that women with POI did not exhibit any change in total testosterone levels or calculated androgen indices. However, significantly lower levels of DHEAS were found in women with POI. Our findings need confirmation in additional studies with a larger sample of POI women.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Seda Ateş;* ***Design:*** *Serdar Aydın;* ***Control/Supervision:*** *Seda Ateş, Çağlar Çetin;* ***Data Collection and/or Processing:*** *Çağlar Çetin;* ***Analysis and/or Interpretation:*** *Serdar Aydın;* ***Literature Review:*** *Taha Süreyya Firidin;* ***Writing the Article:*** *Seda Ateş;* ***Critical Review:*** *Seda Ateş, Serdar Aydın.*

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