

Androgenic Profile of Women with Premature Ovarian Insufficiency

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Abstract Premature ovarian insufficiency (POI) is a condition characterized by an irreversible decrease in ovarian function outside the normal range for women under 40 years of age. **The purpose of the study** is to assess androgens level in women with POI with different levels of FSH. **Materials and methods.** The main group included 80 women (mean age 28.0 ± 7.2 years) with an idiopathic form of POI. The control group included 35 women (mean age 30.6 ± 8.3 years) with regular menstruation and without ascertained endocrine disorders. **Results:** All women with POI were divided into groups based on ESHRE recommendations, group with FSH level >25 to 40 mIU/mL included 16 women, group with FSH level ≥ 40 mIU/mL included 49 patients. On average, in patients with POI, the level of DHEAS and T was statistically significantly lower than in the control group, respectively, but within the laboratory reference values. The level of SHBG and FAI did not differ in women with POI and in the control group, respectively. Similarly, no differences were found between POI subgroups. Diagnostically significant cut-off points were determined for DHEAS (187.5 $\mu\text{g/dl}$), SHBG (51.3 nmol/l), T (0.63 nmol/l) and FAI (0.64). DHEAS (AUC 0.640), T (AUC 0.674) and FAI (AUC 0.632). The level of DHEAS (20.0% , 18.8% , and 20.4%) and T (20.0% , 25.0% , and 22.4%) were significantly lower in some patients than markers cut-off points in prePOF, early POF and POI groups, respectively. However, no significant difference was found between the groups. **Conclusion:** With the help of ROC analysis, diagnostically significant cut-off points for DHEAS, SHBG, T and FAI were determined. It was found that DHEAS (AUC 0.640), T (AUC 0.674) and FAI (AUC 0.632) had a medium diagnostic and prognostic value. Despite the low prognostic significance, androgens shall be taken into account as one of the factors in the development of cardiovascular diseases.

Keywords Premature ovarian insufficiency, Androgenic profile, Risk groups

1. Introduction

Premature ovarian insufficiency (POI) is a condition characterized by an irreversible decrease in ovarian function outside the normal range for women under 40 years of age [1].

According to some researchers, POI exists as a continuum of changes in ovarian function, which includes a "latent" state in which women have reduced fertility, but have normal FSH levels and regular menstruation, a "bio-chemical" state with reduced fertility, elevated FSH levels, but regular menstruation and finally a "clear" condition with reduced fertility, elevated FSH levels, and irregular or no menstruation [2,3,4,5].

According to the literature, in women with POI, a decrease in ovarian production of estradiol and progesterone is sometimes accompanied by a decrease in the level of

circulating androgens compared with women with normal ovarian function [6,7,8,9,10].

Androgens play a significant physiological role in women, acting both as precursors to estrogen biosynthesis and directly through androgen receptors. The most significant biologically active androgen is testosterone (T), which circulates in close connection with sex hormone binding globulin (SHBG) synthesized in the liver. Approximately 78-80% of androgens bind to SHBG, about 19-20% to albumin, and only a small part of testosterone (1-3%) circulates freely in the blood and shows biological activity [10,11].

Some authors have suggested that premature cessation of ovarian function can lead to a hypoandrogenic state. Since hypoandrogenism is associated with a decrease in estrogen concentration (a decrease in the peripheral conversion of testosterone to E2 by fat tissue) and, possibly, with a deterioration in well-being and sexual health, as well as an increased risk of cardiovascular disease [7,12,13].

Androgen deficiency in women is characterized by

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decreased libido, poor health, depression, decreased muscle mass and prolonged causeless fatigue [14]. Glucocorticoids, androgens, growth hormone, synthetic progestins, insulin contribute to a decrease in the content of SHBG in the blood. SHBG concentration in plasma increases by 5-10 times under the influence of estrogens and decreases by 2 times under the influence of testosterone [11].

2. Purpose of the Study

The purpose of the study was to assess androgens level in women with POI with different levels of FSH.

3. Materials and Methods

The main group included 80 women (mean age 28.0 ± 7.2 years) with an idiopathic form of POI. The control group included 35 women (mean age 30.6 ± 8.3 years) with regular menstruation and without ascertained endocrine disorders. All women in the study signed an informed consent to an anonymous analysis of their medical data.

According to ESHRE recommendations, the diagnostic criteria for POI are: oligo / amenorrhea for at least 4 months and elevated FSH level >25 IU / l in two cases with an interval of >4 weeks [15].

Blood sampling was performed in the follicular phase (3-5th day of the menstrual cycle) in controls and against the background of amenorrhea in women with suspected POI.

The levels of hormones in the blood serum were determined (FSH, DHEAS, SHBG and T) by the electrochemiluminescent method on the immunochemical analyzer Elecsys and cobas e. using standard Cobas Roche kits («Roche Diagnostics GmbH», Germany).

The normal reference ranges used in our laboratory were as follows: FSH: 3.5–12.5 mIU/ml; DHEAS: 60.9–407.0 $\mu\text{g/dL}$; SHBG: 32.4–128.0 nmol/L; T: 0.29–1.67 nmol / L. FAI indicator was calculated by the formula: $\text{Testosterone} \times 100 / \text{SHBG}$.

4. Statistical Analysis

Statistical processing of the results was carried out using programs Microsoft Excel, IBM SPSS Statistica 23 and MedCalc version 18.5. The initial data were evaluated for compliance with the normal distribution according to Kolmogorov-Smirnov criterion. Dependences were analyzed using Spearman's rank correlation coefficients. To assess the prognostic significance of markers, ROC analysis (Receiver Operating Characteristic) was used, with the calculation of the area under curve AUC (area under the curve), Se (sensitivity) and Sp (specificity) of the model. Results are presented as median (Me) [interquartile range Q25; Q75]. Differences were considered statistically significant at $p < 0.05$.

5. Results and Discussion

All women with POI were divided into groups taking into account ESHRE recommendations, the group with FSH level >25 to 40 mIU / ml included 16 women, the group with FSH level ≥ 40 mIU / ml included 49 patients.

Since the maximum reference range of FSH in our laboratory was 12.5 mIU/ ml, the study included women under 40 years of age with menstrual disorders (secondary amenorrhea lasting 6 months or more), with FSH level <25 mIU / ml, high LH level and low E2 level, obtained twice with an interval of 4 weeks, AMH concentration of was also taken into account. We identified this cohort of women ($n = 15$) as a group of high risk of premature ovarian failure – POF (mean age 28.7 ± 8.0 years), they did not take medications (for 6 months before the examination), which could affect hormonal and biochemical indicators.

Thus, 3 groups of patients were identified: group 1 of high-risk- POF precursor (prePOF) - FSH <25 mIU / ml ($n=15$), group 2- early POF (earlyPOF - FSH 25-40 mIU / ml ($n=16$) and Group 3- POF with FSH ≥ 40 mIU/ml ($n=49$). It should be noted that the majority (61.3%) of women with POF had FSH level ≥ 40 mIU/ml.

Kalantaridou S. et al. [8] believe that androgens play an important biological role in women in maintaining bone mass and normal sexual function. According to the authors, androgen deficiency may explain a significant decrease in mineral density of bony tissue even against the background of standard estrogen/progestogen hormone therapy in two-thirds of young women with spontaneous POI. A significant factor affecting T clearance is the level of SHBG, which binds T and reduces its free fraction.

The analysis revealed no differences in age and BMI between the three groups. The age of the examined patients and persons from the control group ranged from 18 to 45 years. Age of onset of menarche, age of menstrual disorder, age of onset of amenorrhea did not differ significantly between the groups. Nevertheless, menstrual disorder and amenorrhea were noted in early POF and POI groups approximately 1.5-2 years earlier than among patients with prePOF. (Table 1.).

Studies have shown that, on average, in patients with POI, the level of DHEAS (154.5 ± 70.1 $\mu\text{g/dl}$ and 203.8 ± 83.0 $\mu\text{g/dl}$) and T (0.44 ± 0.25 nmol/l and 0.67 ± 0.39 nmol/l) was statistically significantly lower than in the control group, respectively, but within the laboratory reference values.

If we consider the values of these hormones depending on the level of FSH, then significant differences were noted in groups with early POF and POI compared with the control. However, no difference was found between the subgroups of POI. (Fig.1.).

SHBG level (61.1 ± 28.4 nmol/l and 62.7 ± 21.4 nmol/l) and FAI indicator (0.91 ± 0.8 and 1.19 ± 0.8) in women with POI and control groups did not differ accordingly. Similarly, no differences were found between POI subgroups.

In order to predict pre-POF, cut-off points of such markers

as DHEAS: F, T, SHBG and FAI indicator were determined.

In our study, T has medium prognostic value (AUC 0,674; 95% CI 0.580–0.758; p=0,002; cut-off point 0,63 nmol/l; Se - 0,813; Sp - 0,513) and DHEAS (AUC 0,640; 95% CI 0,546–0,728; p=0,02; cut-off point 187,5 µg/dL; Se - 0,571; Sp - 0,713) and FAI (AUC 0,632; 95% CI 0,537–0, 720; p=0,02; cut-off point 0,64; Se - 0,513; Sp - 0,689). SHBG (AUC 0,546; 95% CI 0,451–0,639; p=0,40; cut-off point 51,3 nmol/l; Se - 0,686; Sp - 0,450) had low prognostic value (Fig. 2.).

Next, the frequency of occurrence of indicators below the

cut-off point for each marker was analyzed. (Fig.3.)

In the course of the study, it was found that in some patients, the level of DGAES (20.0%, 18.8% and 20.4%) and T (20.0%, 25.0% and 22.4%) was significantly lower than the cut-off points of markers in the groups of prePOF, earlyPOF and POI, respectively. However, no significant difference was found between the groups. There was no correlation between these indicators (r = 0.16; p = 0.09), as well as between SHBG and DHEAS (r=0,07; p=0,43) and T (r=-0,06; p=0,55).

Table 1. Clinical and hormonal characteristics of the examined patients

N	Parameter	POI			Control, n=35
		prePOI	earlyPOI	POI	
		FSH <25 mIU/ml, n=15	FSH 25-40 mIU/ml, n=16	FSH ≥40 mIU/ml, n=49	
1	Age, year	28,0; 22,5-32,5	26,0; 23,0-34,8	26,0; 21,0-33	30,0;23,0-38
2	BMI, kg/m ²	29,3; 24,6-33,4	27,1; 18,6-29,1	24,6; 22,5-27,9	24,9;23,3-27,4
3	Age of menarche onset, years	12,5; 11,5-14,0	12,8; 11,9-14,0	13,0; 12,6-14,3	12,0; 11,0-13,0
4	Age of amenorrhea onset, years	24,0; 18,0-28,0	21,0; 14,8-26,3	22,0; 16,0-27,0	-
5	DHEAS, µg/dL	155,4; 109,4-188,3	109,6; 81,8-165,4*	149,2; 98,5-198,8*	198,7; 118,6-285,2
6	SHBG, nmol/L	55,6; 36,5-67,1	48,4; 38,6-68,9	59,7; 45,4-87,9	58,8; 48,7-75,6
7	T, nmol/ L	0,49;0,21-0,88	0,48;0,24-0,58*	0,35;0,20-0,54*	0,66; 0,34-0,96
8	FAI	0,94;0,36-1,44	0,76;0,51-1,36	0,53;0,38-1,0	1,06;0,64-1,52

Data presented in the form data are presented in the form of Me and IQR; * - reliability in relation to control. POI: premature ovarian insufficiency; POF: premature ovarian failure; MD: menstrual disorder; BMI - body mass index; DHEAS: dehydroepiandrosterone sulfate; SHBG: sex hormone-binding globulin; T: testosterone; FAI: free androgen index.

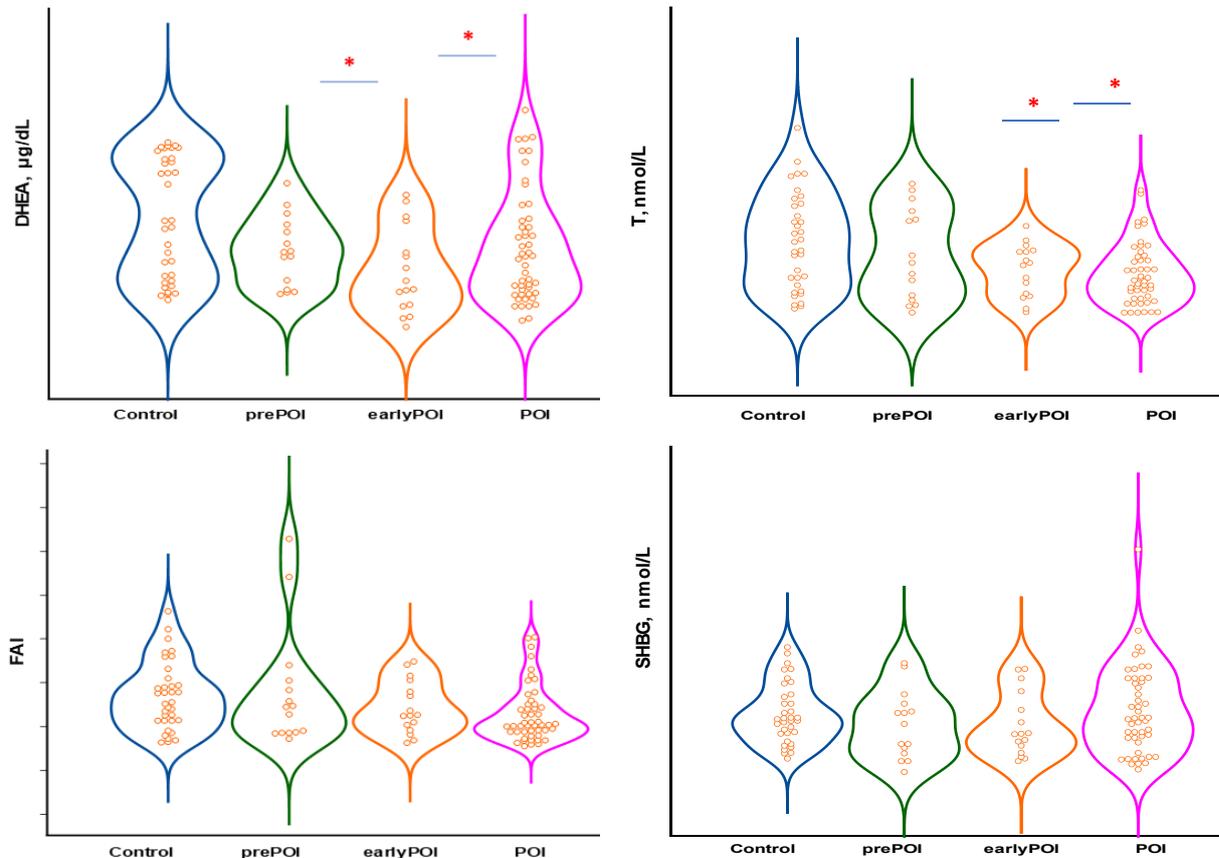


Figure 1. Changes in androgenic status at various stages of ovarian insufficiency

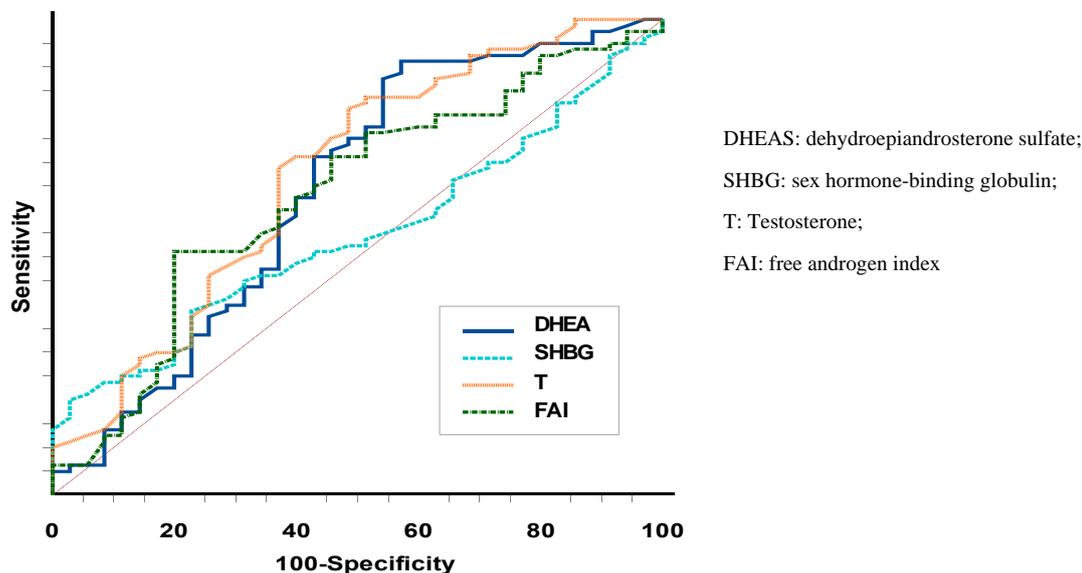


Figure 2. ROC-curves for forecasting POI

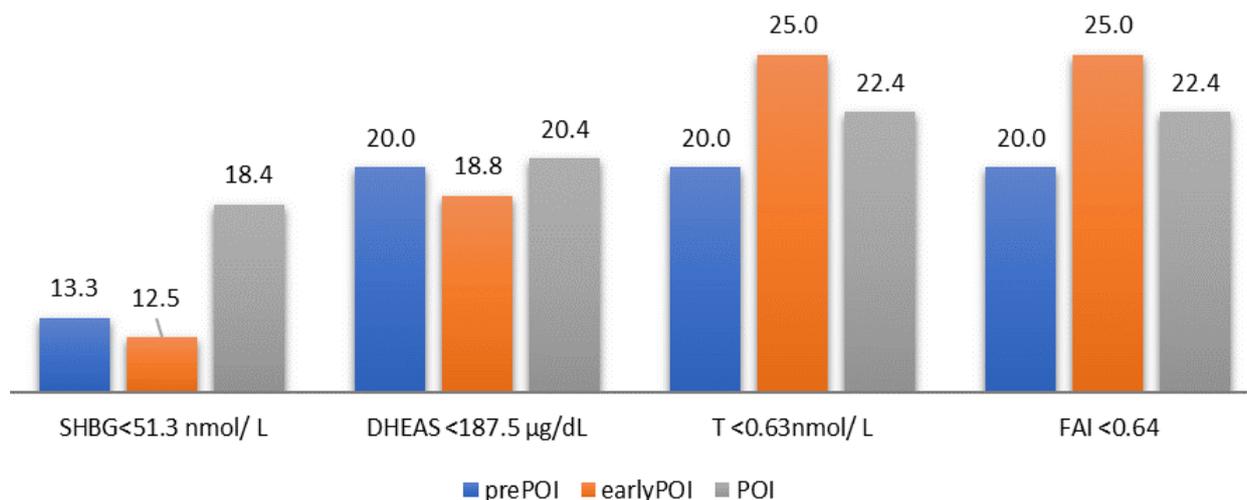


Figure 3. The occurrence of androgens and FAI below the cut-off point in patients with POI, in %

According to the results of the study of Janse F. et al. [7] women with spontaneous POI had lower T concentrations than women in the control group (weighted average difference -0.38 nmol/L; 95% CI -0.55 to -0.22 nmol/L). The authors suggest that premature cessation of ovarian function can lead to a hypoandrogenic state. A decrease in circulating testosterone can occur as a result of atrophy of the reticular zone of the adrenal glands (a decrease in the synthesis of T precursors), which in turn leads to a decrease in the peripheral conversion of dehydroepiandrosterone sulfate (DHEA-C) (via DHEA) to testosterone [16,17].

6. Conclusions

With the help of ROC analysis, diagnostically significant cut-off point was determined for DHEAS (187.5 µg / dL), SHBG (51.3 nmol / L), T (0.63 nmol / L) and AAI (0.64). DHEAS (AUC 0.640), T (AUC 0.674) and ISA (AUC 0.632)

had average diagnostic and prognostic value. Despite the low prognostic significance, androgens shall be taken into account as one of the factors in the development of cardiovascular diseases.

Conflict of interest: The author has no conflict of interest to declare.

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