Anti-Müllerian hormone: plasma levels in women with polycystic ovary syndrome and with premature ovarian failure

Stężenie hormonu antymüllerowskiego w surowicy u kobiet z zespołem policystycznych jajników i w zespole przedwczesnego wygasania czynności jajników

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Summary

Background: Anti-Müllerian hormone (AMH) is a member of the transforming growth factor β (TGF-β) family of growth and differentiation factors. AMH is produced by granulosa cells of preantral and small antral follicles.

Aim of the study: The aim of the study was to assess the AMH plasma levels of healthy women in reproductive age and in women with polycystic ovary syndrome (PCOS) and premature ovarian failure (POF).

Material and methods: The study included 187 women.

Results: AMH concentration in serum of patients with PCOS (73.68 ±25.58 pmol/l) was significantly higher than in healthy women (16.97 ±5.80 pmol/l) ($p < 0.05$). In patients with POF AMH concentrations in blood serum were very low or undetectable, and averaged 0.65 ±1.81 pmol/l. Average concentrations of AMH in the blood serum of the healthy group of patients differed significantly ($p < 0.001$) between the age-dependent subgroups. AMH concentration in serum of healthy women decreased with age. The average concentration of AMH in the blood serum in PCOS decreased after 30 years of age. There were no statistically significant differences between age subgroups.

In the premature ovarian failure patients with secondary amenorrhea persisting for at least three years AMH plasma levels were extremely low (0.16 ±0.10 pmol/l) and showed a significant difference compared to patients whose menses returned.

Conclusions:

1. In PCOS women the determination of AMH plasma levels can be used to assess severity of the syndrome.
2. The determination of AMH in blood serum can be used as a marker of diminished ovarian reserve in premature ovarian failure women.

Key words: anti-Müllerian hormone, polycystic ovary syndrome, premature ovarian failure.

Streszczenie

Wstęp: Hormon antymüllerowski (AMH) należy do nadrodziny peptydowych czynników wzrostu i różnicowania czynnika wzrostu β (*transforming growth factor β* – TGF-β). Hormon antymüllerowski jest produkowany przez komórki ziarniste jajnika.

Cel pracy: Celem badań jest ocena stężeń AMH w surowicy u zdrowych kobiet w okresie rozrodczym oraz u kobiet z zespołem policystycznych jajników (*polycystic ovary syndrome* – PCOS) i z zespołem przedwczesnego wygasania czynności jajników (*premature ovarian failure* – POF).

Materiał i metody: Do badań zakwalifikowano 187 kobiet w wieku rozrodczym między 18. a 35. r.ż.

Wyniki: Stężenie AMH w surowicy u kobiet z PCOS wynosiło: 73,68 ±25,58 pmol/l i było znamiennie większe niż u zdrowych kobiet, u których wynosiło ono 16,97 ±5,8 pmol/l ($p < 0,05$). U pacjentek z POF stężenie AMH było bardzo małe lub niewykrywalne (0,65 ±1,81 pmol/l). Stężenie AMH w surowicy u zdrowych kobiet w sposób istotny różniło się między podgrupami wiekowymi. Stężenie to zmniejszało się wraz z wiekiem. Stężenie AMH w surowicy u kobiet z PCOS zmniejszało się dopiero po 30. r.ż. U tych kobiet nie odnotowano istotnych statystycznie różnic pomiędzy podgrupami wiekowymi.

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U pacjentek z POF z wtórnym brakiem miesiączki trwającym dłużej niż 3 lata stężenie AMH w surowicy było znacząco małe lub nieoznaczalne (0,16 ±0,10 pmol/l). U pacjentek z POF, u których nastąpił powrót miesiączkowania, stężenie hormonu było znamiennie większe, lecz istotnie mniejsze niż u zdrowych kobiet.

Wnioski:

1. Stężenie AMH we krwi u kobiet z PCOS może być stosowane w celu oceny ciężkości choroby.
2. Oznaczanie stężenie AMH we krwi może być markerem obniżającej się rezerwy jajnikowej u kobiet z POF.

Słowa kluczowe: hormon antymüllerowski, zespół policystycznych jajników, przedwczesne wygasanie czynności jajników.

Background

Anti-Müllerian hormone (AMH), also called Müllerian inhibiting factor (MIS), is a glycoprotein belonging to the superfamily of peptide growth/differentiation factors TGF-β. AMH is expressed by granulosa cells of the ovary during the reproductive years [1]. It has been demonstrated that granulosa cells of preantral and small antral follicles produced substantial amounts of AMH, which supply the blood [2]. In healthy women from puberty until 25 years, the AMH plasma level does not change significantly, but during the perimenopausal period it is reduced to undetectable values [3]. The situation is similar in women with premature ovarian failure (POF). Therefore, AMH can be considered as a marker of ovarian reserve.

Recently published clinical studies strongly suggest that AMH measures are useful in assessing conditions such as polycystic ovary syndrome (PCOS) and POF [4].

Aims of the study

The aim of the study is to assess changes in AMH plasma levels of healthy women of reproductive age and compare them with changes observed in PCOS women of similar age. The aim of the study is also to review AMH plasma levels as a marker of ovarian reserve based on the results of hormone determinations in POF women.

Material and methods

The study included 187 women of reproductive age between 18 and 35 years of age who were hospitalized in the Department of Gynaecological Endocrinology, Medical University of Silesia in Katowice or were seen in the Outpatient Clinic for follow-up and contraceptive advice in the period from 01.01.2008 until 31.12.2009.

The women were divided into 3 groups: group 1, healthy women; group 2, diagnosed with PCOS; and group 3, diagnosed with POF.

Group 1 consisted of 50 healthy women. Criteria for inclusion in the study for this group were as follows: a regular menstrual period, have at least one child and normal concentrations of serum follicle stimulating hormone (FSH), E2, free testosterone, total testosterone, androstenedione, 17-OHP and DHEAS.

Group 2 consisted of 90 patients diagnosed with PCOS. The criterion for inclusion in this group was identification of PCOS.

Criteria for exclusion from the study, for both groups, were as follows: hormonal therapy in the past 6 months, use of other drugs that may affect the hormonal and metabolic profile of patients, for example, antiepileptic drugs, and the presence of other endocrinopathies.

Patients of the above two groups were divided according to age into 3 subgroups in the ranges: 18-23 years, 24-29 years, 30-35 years.

Group 3 consisted of 47 patients with POF. Criteria for inclusion in this group were as follows: age between 18 and 40 years, secondary amenorrhea, concentration of serum FSH > 40 IU/ml determined twice at intervals of one month and concentration of serum oestradiol < 110 pmol/l. Exclusion criteria for this group were the same as for the other two groups, and additionally included the following: disorders of the sex chromosomes, hyperprolactinaemia, hormone therapy within the last 3 months, and Addison's disease.

POF patients were divided into two subgroups: (1) 39 patients with secondary amenorrhea persisting for at least three years, (2) 8 patients with menstrual rhythm that has been observed to return to the correct type or oligomenorrhoea and normalization of E2 and FSH concentrations in blood serum.

PCOS was diagnosed according to the Rotterdam criteria [5].

All women included in the study underwent assessment of anthropometric parameters (body mass, BMI), standard medical examination, gynaecological examination, and pelvic ultrasound.

In women with preserved menstrual rhythm, hormonal tests were performed in the first phase of the cycle between days 3 and 5 of the cycle. In women with secondary amenorrhea, the progesterone test was performed and the samples were taken between 3 and 5 days after the appearance of bleeding.

In order to perform hormonal tests 10 ml of venous blood were collected from each patient, centrifuged and the serum frozen and stored at –70°C until tested, but not longer than 30 days. Then the serum was thawed slowly at room temperature and the following were determined: AMH, FSH, luteinizing hormone (LH), oestradiol (E2), prolactin (PRL), thyrotropin (TSH), free thyroxine (fT4), free testosterone (Tw), total testosterone (T),

androstenedione, cortisol, sulfate dehydroepiandrosterone (DHEAS), 17-hydroxyprogesterone (17-OHP) and sex hormone binding globulin (SHBG).

The results of hormone determinations, with the exception of AMH, are not analysed in this study, but were used only for confirming the diagnosis.

Results

All tested groups of women were homogeneous in terms of age, height, weight and BMI. AMH concentration in serum of patients with PCOS (73.68 ±25.58 pmol/l) was significantly higher than in healthy women (16.97 ±5.89 pmol/l) ($p < 0.05$). In patients with POF AMH concentrations in serum were very low or undetectable (0.65 ±1.81 pmol/l; Table I).

Anti-Müllerian hormone concentration in serum of healthy women decreased with age. In the age range 18-23 the value was 24.15 ±0.66 pmol/l. In the age range 24-29 it was 18.13 ±1.61 pmol/l. In the age range 30-35 it was 10.32 ±1.14 pmol/l. Average concentrations of AMH in the blood serum of healthy patients differed significantly ($p < 0.001$) between age subgroups (Figure 1).

The average concentration of AMH in the blood serum in PCOS decreased after 30 years of age. In the age range 18-23 the value was 76.68 ±28.05 pmol/l. In the age range 24-29 it was 76.04 ±22.57 pmol/l. In the age range 30-35 it was 64.34 ±22.33 pmol/l. There were no statistically significant differences between age subgroups (Figure 2).

In patients with POF, AMH concentration in serum was significantly lower than in healthy women. In the subgroup of patients with secondary amenorrhea persisting for at least 3 years the value was 0.16 ±0.10 pmol/l. In the subgroup of patients who were observed to return to normal menstrual rhythm or rare menstruation and normalization of E2 and FSH concentrations in serum, AMH was 3.06 ±3.69 pmol/l. A significant difference ($p < 0.001$) was observed in AMH serum concentrations between patients from these two subgroups (Figure 3).

Tab. I. Anti-Müllerian hormone concentration in blood serum in women with polycystic ovary syndrome, premature ovarian failure and in the control group

		Healthy women	PCOS	POF
	n	**50**	**90**	**47**
AMH (pmol/l)	mv ±SD	**16.97 ±5.89**	**73.68 ±25.58**	**0.65 ±1.81**
	min	8.54	31.85	0
	max	25.27	125.65	7.7
		$p < 0.001$		
			$p < 0.001$	
				$p < 0.001$

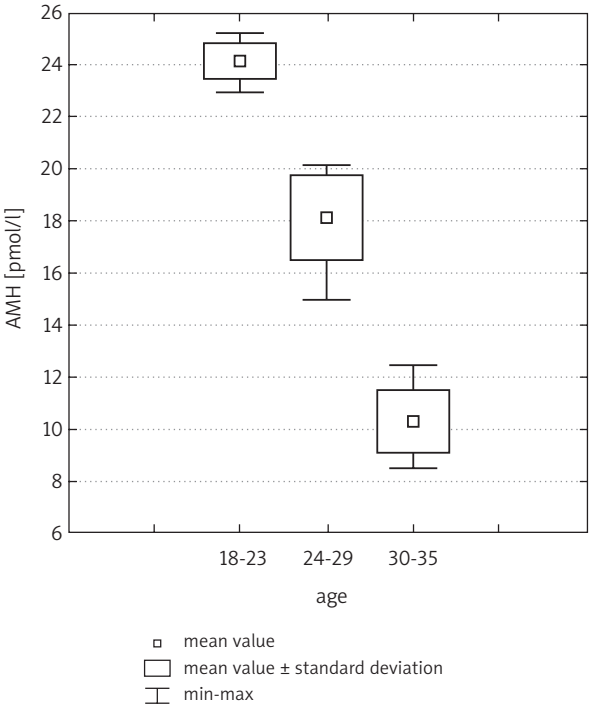

Fig. 1. Anti-Müllerian concentration in blood serum in women in the control group

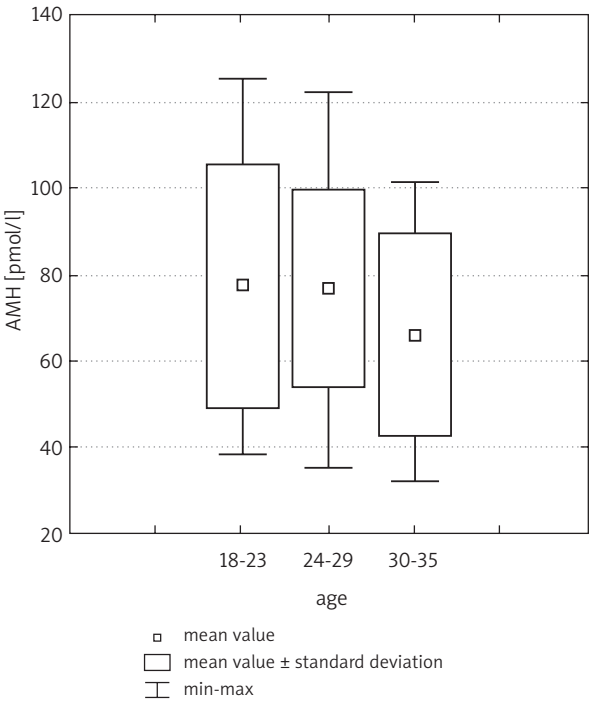

Fig. 2. Anti-Müllerian hormone concentration in blood serum in women with polycystic ovary syndrome

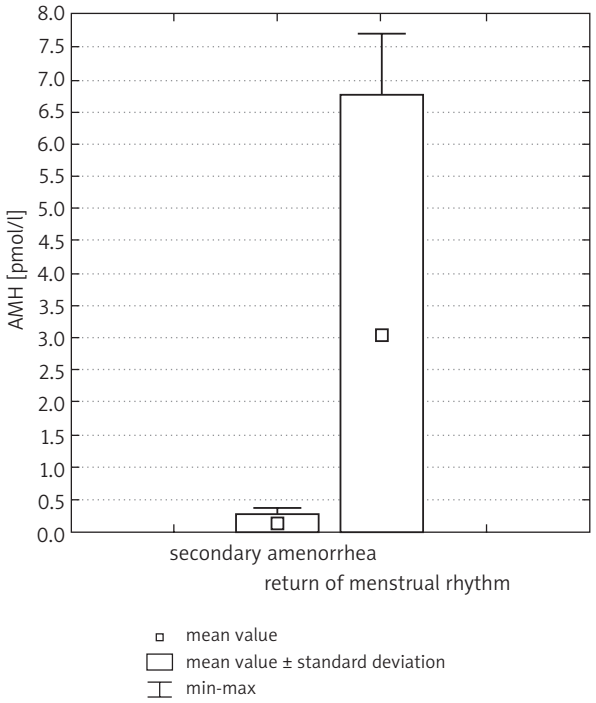

Fig. 3. Anti-Müllerian concentration in blood serum in women with premature ovarian failure

Discussion

Premature ovarian failure is a heterogeneous disorder with multicausal pathogenesis. Underlying the disorder is premature exhaustion of the resting pool of primordial follicles.

Ovarian insufficiency might take several years to develop. Temporary improvement might happen in some women, as noted by periods of low FSH plasma levels, and menstruation. Such a situation is referred to as "transitional ovarian failure" [6]. Patients with this diagnosis have a chance of becoming pregnant. It is estimated to concern about 10% of them. Therefore, to assess the chances of becoming pregnant it is important to identify the size of the ovarian reserve. Recent studies suggest that AMH may offer improved specificity in predicting ovarian response and pregnancy changes. The presented results show that in women with POF, AMH plasma levels are significantly lower than in healthy women. Tests so far have shown that AMH is undetectable in 83% of women with POF. The remaining 17% have low plasma levels of AMH. The results obtained allow one to recognize in this subgroup of patients "transitional ovarian failure" and assess their individual chances of becoming pregnant. Our results seem to confirm the determination of AMH in the blood as a good test evaluating ovarian reserve – especially because this parameter has the advantage over FSH of not being affected by cyclic variation [6-8].

The present study confirmed a significant increase in AMH concentrations in the blood serum of patients with PCOS compared to healthy women of similar age, which is consistent with the literature data [9-11]. It was proved that AMH is expressed in pre- and small antral follicles [12]. In PCOS women AMH plasma levels are high, in accordance with their increased amount of small follicles. It was also found that the plasma level of AMH correlated with serum concentration of testosterone and LH [13]. It is believed that AMH levels reflect the severity of PCOS [14].

Considering the facts cited above, we can hypothetically suppose that increased AMH levels in women with PCOS do not seem to be merely the result of increased numbers of small follicles per se or increased androgen levels alone. Determination of the concentration of AMH in the blood is not only a proper test of ovarian reserve evaluation, but also an important procedure in the diagnosis of PCOS. It was recently suggested that the determination of the AMH plasma levels and sonographic assessment of the antral follicle count (AFC) have become the criteria for PCOS diagnosis [15].

An interesting finding is that the decrease in AMH levels in serum of patients with PCOS occurs later than in healthy women [16]. In the present study we found that average concentrations of AMH in the blood serum in PCOS decreased after 30 years of age, as compared to healthy women, who have lower levels of the hormone after 23 years of age.

This relationship does not apply to the same degree in the PCOS women as in their healthy peers. So we can assume that women with PCOS retain a greater ovarian reserve longer. We think so, although it probably does not increase their chances of conceiving later in life.

Conclusions

In PCOS women the determination of AMH plasma levels can be used to assess severity of the syndrome.

The determination of AMH in blood serum can be used as a marker of diminished ovarian reserve in premature ovarian failure women.

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