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Anti-Müllerian Hormone Serum Concentrations in Normoovulatory and Anovulatory Women of Reproductive Age

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Anti-Müllerian hormone (AMH) concentrations correlate with the number of antral follicles as well as age and constitute an endocrine marker for ovarian aging. In normogonadotropic anovulatory infertile women [World Health Organization (WHO) class 2], the number of early antral follicles is usually increased. To investigate whether AMH concentrations are increased, serum levels in 128 WHO 2 women were compared with those in 41 normoovulatory premenopausal women of similar age.

Serum AMH concentrations are significantly ($P < 0.001$) elevated in WHO 2 patients [median, 7.6 μg/liter (range, 0.1–40.0)], compared with controls [median, 2.1 μg/liter (0.1–7.4)]. In 106 patients presenting with polycystic ovaries (PCOs) (≥12 follicles/ovary measuring 2–9 mm and/or an ovarian volume > 10 ml), AMH levels were elevated [9.3 μg/liter (1.8–40.0)], compared with 22 patients without PCOs [6.4 μg/liter (0.1–22.1)] ($P < 0.0001$). In WHO 2 patients, AMH concentrations correlated with features characteristic for polycystic ovary syndrome such as LH concentrations ($r = 0.331$; $P = 0.0001$), testosterone levels ($r = 0.477$, $P = 0.0001$), mean ovarian volume ($r = 0.421$; $P = 0.0001$), and the number of ovarian follicles ($r = 0.308$; $P = 0.0001$). AMH levels correlated well with age in WHO 2 patients ($r = -0.248$; $P = 0.002$) as well as in controls ($r = -0.465$; $P = 0.005$). However, the relative decline in AMH with age is less pronounced in WHO 2 patients. In a subset of patients no significant correlation was found between AMH serum concentrations and the FSH response dose, the duration of stimulation, and the total number of ampoules of FSH used.

In conclusion, serum AMH concentrations are elevated in WHO 2 women, especially in those patients exhibiting PCOs. Because AMH concentrations correlated well with other clinical, endocrine, and ultrasound markers associated with polycystic ovary syndrome, AMH may be used as a marker for the extent of the disease. A less pronounced AMH decrease over time in these women may suggest retarded ovarian aging. The latter hypothesis, however, should be confirmed by longitudinal studies. (*J Clin Endocrinol Metab* 89: 318–323, 2004)

THE DIMERIC GLYCOPROTEIN anti-Müllerian hormone (AMH), also referred to as Müllerian-inhibiting substance, is a member of the TGFβ superfamily (1). During fetal sex differentiation, AMH is produced by Sertoli cells in the male, in which it induces degeneration of the Müllerian ducts (2). In females, AMH is expressed only postnatally by the ovary, and until recently its function in the female reproductive tract was unknown (3, 4).

Female AMH null mice were reported to be fertile and produced normal-sized litters (5). However, ovaries of AMH null mice as well as female mice heterozygous for the AMH null mutation contained less primordial follicles and more growing follicles, compared with their wild-type littermates (6). In addition, AMH was able to inhibit the initiation of primordial follicle growth in cultured neonatal mouse ovaries (6) and stimulate growth of rat preantral follicles (7). Hence, AMH appears to regulate early follicle development directly. Furthermore, the absence of AMH has been shown to enhance FSH-induced follicle growth in female mice (8).

Abbreviations: AD, Androstenedione; AMH, anti-Müllerian hormone; E_2, estradiol; PCO, polycystic ovary; PCOS, PCO syndrome; T, testosterone.

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Recently serum AMH levels have been shown to decrease over time in young normoovulatory women, whereas other markers associated with ovarian aging did not change during this time interval (9). Although AMH concentrations did correlate with age and FSH, AMH serum levels were most strongly associated with the number of antral follicles. Therefore, AMH might represent a sensitive marker for ovarian aging (10). Indeed, it has been shown that poor response during *in vitro* fertilization, indicative of a diminished ovarian reserve (11), is associated with reduced baseline serum AMH concentrations (12, 13).

Chronic anovulation constitutes a major (20–25%) proportion of infertile couples (14, 15). According to the World Health Organization (WHO), approximately 80% of patients suffering from chronic anovulation present with serum FSH levels within the normal range along with normal endogenous estrogen activity. These women are classified as having normogonadotropic normoestrogenic anovulatory infertility, more commonly referred to as WHO class 2 (16). Because etiologic factors underlying this condition may vary from one patient to another, WHO 2 anovulatory women including those with polycystic ovary syndrome (PCOS) constitute a notoriously heterogeneous population (17). In WHO 2 patients, the number of small antral follicles is generally increased due to disturbed dominant follicle selection (18).

Because AMH is predominantly expressed by small follicles in mice (4) as well as in the human (19), AMH serum concentrations may be increased in patients with polycystic ovaries (PCOs). Indeed, in PCOS patients exhibiting the classical features of the syndrome, AMH levels were found to be elevated, compared with normal controls (20). The current study was designed to evaluate AMH as a clinically relevant marker for the extent of ovarian dysfunction in WHO 2 anovulatory women, with or without PCOs.

Subjects and Methods

Subjects

The local Medical Ethics Review Committee approved this study, and informed consent was obtained from all participants. Included in the present study were 128 patients attending our fertility clinic between 1994 and 1999 with the following: 1) infertility; 2) oligomenorrhea (interval between periods >35 d) or amenorrhea (absence of vaginal bleeding for at least 6 months); 3) serum FSH concentrations within normal limits (1–10 IU/liter) (21); 4) positive withdrawal bleeding after progestogen administration in case of amenorrhea; and 5) age between 19 and 41 yr. Standardized initial screening [clinical investigation, transvaginal ultrasound, and fasting blood withdrawal] was performed on a random day between 0900 and 1100 h, irrespective of the interval between blood sampling and the preceding bleeding, as previously described (22). A subgroup of these patients was diagnosed with PCOS due to hyperandrogenemia and an increased follicle number and/or ovarian volume. Hyperandrogenemia was defined as an elevated (>4.5) free androgen index (testosterone × 100/ SHBG). Similarly, an increased follicle number was defined as 12 follicles or more per ovary measuring 2–9 mm, and the ovarian volume was considered to be increased above 10 ml (15).

For sonographic imaging, we used a 6.5 MHz vaginal transducer (model EUB-415, Hitachi Medical Corp., Tokyo, Japan). The ovaries were localized and scanned as described previously (23). Ovarian volume, stroma echogenicity (arbitrarily scored from 1 to 3 per ovary), and the mean follicle number were assessed as described earlier (15). Women exhibiting PCOs had either an increased ovarian volume (>10 ml) or an increased number of follicles (≥12 follicles measuring 2–9 mm in at least one ovary).

The control group consisted of 41 healthy volunteers selected by advertisement and paid for participation as previously published (21). Inclusion criteria were a regular menstrual cycle (26–30 d), age of 20–36 yr, normal body mass index (18–25 kg/m^2), and no previous use of medication or oral contraceptives during at least 3 months before the study. Transvaginal ultrasound and blood sampling was performed during the early follicular phase (cycle d 3, 4, or 5).

Ovulation induction treatment

In a subgroup of WHO 2 women (those who failed to ovulate or conceive after clomiphene citrate treatment), gonadotropin treatment was commenced within 3–5 d after initiation of a spontaneous or progestogen-induced withdrawal bleeding. Patients received daily sc injections of recombinant FSH (Gonal-F, Ares-Serono, Geneva, Switzerland). During all first cycles, a low-dose step-up protocol was used with a starting dose of FSH of one ampoule (75 IU) per day. The daily dose was increased by ½ ampoule if ovarian response (at least one follicle of at least 10 mm) was absent after 14 d. Thereafter the dose was increased by ½ ampoule every 7 d if required. The FSH response dose was defined as the dose at which an ovarian response was observed (24). In case a sufficient ovarian response was observed, the dose was kept constant until administration of 5000 IU human chorionic gonadotropin (Profasi, Ares-Serono).

Hormone assays

Blood samples were obtained by venepuncture and processed within 2 h after withdrawal. Serum was stored at −20 C and assayed for AMH, LH, FSH, androstenedione (AD), testosterone (T), SHBG, inhibin B, and estradiol (E_2). Serum AMH levels were assessed using an ultrasensitive immunoenzymometric assay (Immunotech-Coulter, Marseilles, France), as described elsewhere (9). The limit of detection (defined as blank +3 SD of the blank) amounted to 0.05 μg/liter. For quality control, samples of pooled serum with high and low levels of AMH were assayed in all separate assays. Intra- and interassay coefficients of variation were less then 5% and 8%, respectively.

Serum levels of LH, FSH, and SHBG were measured using luminescence-based immunoassays (Immulite, Diagnostic Products Corp., Los Angeles, CA), whereas serum E_2, T, and AD levels were measured using coated-tube RIAs provided by the same supplier. Intra- and interassay coefficients of variation were less than 5% and 15% for LH, less than 3% and 8% for FSH, less than 8% and 11% for AD, less than 3% and 5% for T, less than 5% and 7% for E_2, and less than 4% and 5% for SHBG, respectively.

Dimeric inhibin B levels were assessed using an immunoenzymometric assay obtained from Serotec (Oxford, UK), as described previously (21). The detection limit of the assay, defined as the amount of inhibin equivalent with the signal of the blank +3 SDs of this signal, was 3.4 ng/liter. Intra- and interassay coefficients of variation for inhibin B were less than 9% and 15%, respectively.

Data analysis

Statistical analysis was performed using a commercially available software package (SPSS, SPSS Inc., Chicago, IL). Data were analyzed for normal distribution. Data are presented as the mean ± SD if distributed normally or otherwise as the median and range. To determine differences between groups, Mann-Whitney *U* or Kruskal-Wallis tests were used if data were not normally distributed. In case data were normally distributed, Student's *t* test or ANOVA was used. Correlations were expressed as Spearman's correlation coefficients. Regression statistics were applied to assess the differences in decline of parameters in time. $P \leq 0.05$ was considered to be statistically significant.

Results

General clinical characteristics and endocrine data as well as ultrasound findings in controls and patients are summarized in Table 1. Briefly, patients were comparable with control subjects as far as age was concerned. Endocrine parameters in control subjects were all well within the normal range for regularly cycling women. Similarly ultrasound scans revealed normal follicle counts in both ovaries in these volunteers.

WHO 2 patients were either oligo- or amenorrheic, with a median cycle duration of 75 d, being significantly different ($P < 0.001$) from controls. The body mass index was significantly different in WHO 2 women, compared with controls ($P < 0.01$). WHO 2 women presented with elevated LH and T and more PCOs on ultrasound scanning.

AMH levels were significantly ($P < 0.001$) different between controls (median 2.1 μg/liter; range, 0.1–7.1 μg/liter) and WHO 2 patients (median 7.6 μg/liter; range 0.1–40.0 μg/liter). When WHO 2 women were categorized into those with and without PCOs (≥12 follicles measuring between 2 and 9 mm and/or ovarian volume >10 ml), AMH levels were significantly higher (9.3 μg/liter; range 1.8–40.0 μg/liter) in PCO patients, compared with non-PCO (6.4 μg/liter; range 0.1–22.1 μg/liter; $P < 0.001$) and controls (2.1 μg/liter; range 0.1–7.1 μg/liter; $P < 0.001$) (Fig. 1).

There was a significant ($r = -0.465$; $P < 0.002$) negative correlation between age and AMH levels in control subjects. Similarly, a significant negative correlation was found in WHO 2 patients ($r = -0.248$; $P < 0.001$). The decrease in AMH levels with increasing age was significantly ($P < 0.001$) different in WHO 2 patients, compared with controls (Fig. 2).

TABLE 1. Clinical, endocrine, and ultrasound parameters (median and range) in normoovulatory control subjects compared to normogonadotropic normoestrogenic anovulatory infertile women (WHO 2)

	Controls (n = 42)	WHO 2 (n = 128)
Clinical parameters		
Age (yr)	29.9 (20.6–35.6)	28.9 (19.3–40.8)
BMI (kg/m^2)	21.5 (18.8–24.3)	25.9 (22.1–39.8)[a]
Cycle duration (d)	28 (25–31)	75 (35–183)[b,c]
Endocrine parameters		
LH (IU/liter)	3.1 (1.0–6.7)	7.0 (1.1–23.5)[a]
FSH (IU/liter)	6.1 (3.3–10.0)	5.5 (2.3–10.0)
Estradiol (pmol/liter)	153 (64–404)	241 (73–864)
Inhibin B (ng/liter)	113 (12–213)	129 (21–430)
Testosterone (nmol/liter)	1.5 (0.5–2.9)	2.5 (0.7–6.5)[a]
Androstenedione (nmol/liter)	NA	14.1 (4.0–49.3)
FAI	NA	5.9 (1.4–29.3)
Ultrasound parameters		
Mean number of follicles (both ovaries)	14 (6–28)	24.0 (2–45)[a]
Ovarian volume (ml) (per ovary)	NA	10.5 (2.5–22.9)

NA, Not assayed.
[a] $P < 0.01$.
[b] $P < 0.001$.
[c] Amenorrhea.

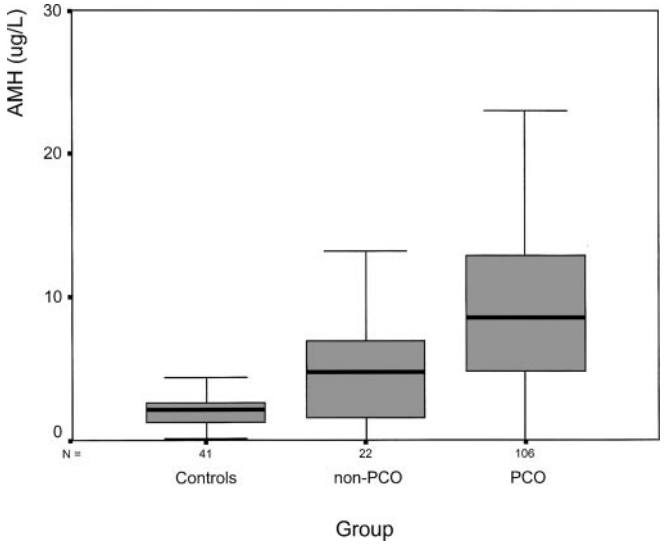

FIG. 1. Box and whisker plots depicting the AMH serum levels in normogonadotropic anovulatory infertile women with PCOs and those without (non-PCO), compared with normoovulatory controls. *Solid lines inside boxes* depict the median AMH level, whereas the *upper* and *lower limits of the boxes* and whiskers indicate 75th, 25th and 95th, and 5th percentiles.

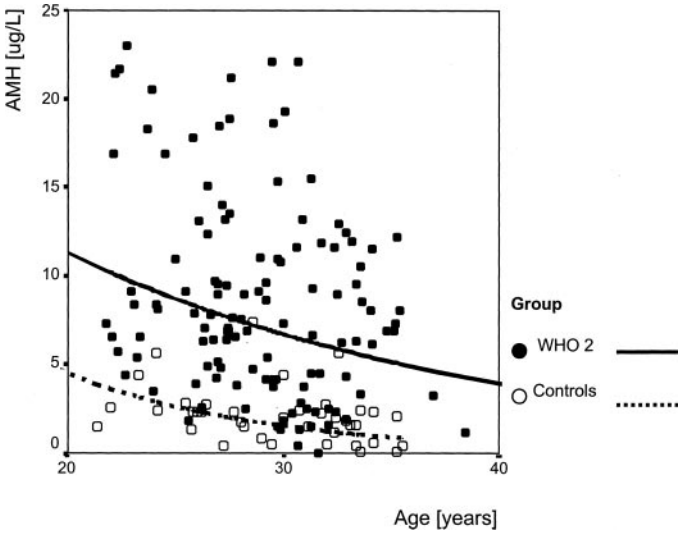

FIG. 2. Individual serum AMH concentrations *vs.* age in 128 WHO 2 anovulatory infertile patients (*closed dots*), compared with 41 normoovulatory controls (*open dots*). Note the differences (in AMH concentration and slope) between the regression lines of WHO 2 and controls.

In WHO 2 patients, AMH levels were significantly correlated with cycle duration (r = 0.203; $P < 0.05$), LH (r = 0.331; $P < 0.001$), T (r = 0.477; $P < 0.001$), AD (r = 0.321; $P < 0.001$), free androgen index (r = 0.224; $P < 0.01$), mean ovarian volume (r = 0.421; $P < 0.001$), and mean follicle number (r = 0.308; $P < 0.001$) but not with inhibin B levels (Fig. 3).

In 79 WHO 2 patients who previously failed clomiphene citrate ovulation induction (75%), data with regard to ovulation induction outcome using gonadotropins were available. There was no significant correlation between AMH serum levels and the FSH response dose, being defined as the dose of exogenous FSH at which the first follicle of 10 mm or larger emerged (r = −0.147; $P < 0.200$; data not shown). Similarly, there was no correlation between AMH serum concentrations and the duration of stimulation (in days) or the total number of ampoules FSH used (data not shown).

Discussion

The present study clearly shows that AMH levels are increased in normogonadotropic anovulatory infertile patients. The subgroup of WHO 2 women exhibiting PCOs presents with the highest AMH serum levels. Furthermore, it seems that AMH levels correlate with the extent of ovarian dysfunction in these women, as represented by elevated LH or T levels and an increased follicle number and/or ovarian volume as established on ultrasound. Finally, it might be hypothesized that the age of menopause is delayed in these anovulatory women, which might be a direct consequence of elevated intraovarian AMH production due to an increased number of AMH-producing units.

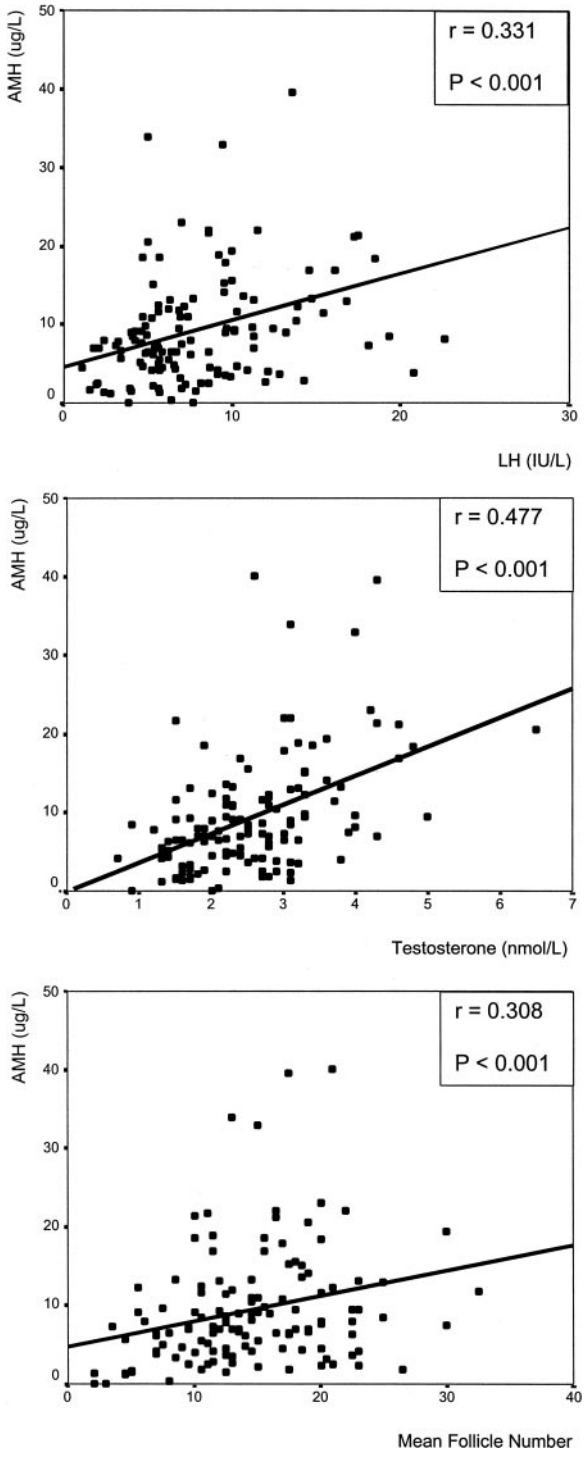

FIG. 3. Scatterplot depicting the relationship between the individual AMH serum concentrations and LH, T, and the mean follicle number, respectively, in WHO 2 anovulatory women. Correlation coefficients and Spearman ranks (r) and their respective significance levels (P) are shown in the *boxes in the upper right corner*.

On histological examination it has been shown that PCOs exhibit the same number of primordial follicles, whereas the number of developing and subsequent atretic follicles was doubled, compared with normoovulatory controls (25). Despite the increased number of developing follicles, inhibin B serum levels (a marker for small developing follicles) were normal in WHO 2 patients, suggesting an increased number of atretic follicles (26). It appears that follicle development is arrested in PCOS at the stage in which dominant follicle selection occurs under normal conditions (27–30). Follicle maturation arrest during later stages of development may lead to a build up of many immature follicles, which in itself could explain increased AMH levels. Hence, it might be anticipated that the increased number of follicles, which are generally present in PCOs, are the source of increased AMH production (20).

Because AMH constitutes a marker for the number of small follicles, its correlation with ovarian volume and the number of follicles present in the ovary, is not surprising. PCOs as observed during ultrasound constitute a sensitive marker for the extent of ovarian dysfunction in anovulatory women as well as for ovulation induction outcome (31, 32). Although AMH serum levels were the highest in anovulatory patients with prominent PCOs, women without PCOs also exhibited elevated levels. In the female, AMH is solely synthesized by granulosa cells of preantral and small antral follicles (4). Apparently, smaller follicles, which are not readily detected on ultrasound, do significantly contribute to serum AMH levels. Therefore, AMH might even constitute a more sensitive marker of ovarian dysfunction in WHO 2 patients than PCO on ultrasound. Indeed, AMH serum levels correlated well with other parameters indicative for the extent of ovarian dysfunction such as elevated LH and T concentrations.

Unfortunately, AMH serum concentrations were not significantly correlated with outcome parameters of ovulation induction using gonadotropins in those women who previously failed clomiphene citrate ovulation induction. Similarly, pregnancy rates and miscarriage rates were similar in patients with moderately and severely elevated AMH serum levels. Hence, elevated AMH serum levels are not associated with adverse treatment outcome, indicating a limited predictive power of AMH levels in these patients. It seems therefore that the clinical relevance of AMH serum concentrations is limited in women in whom clomiphene citrate ovulation induction previously failed.

In PCOS patients, aromatase activity may be decreased because follicles from PCOs do not produce large amounts of E_2. It has been shown that follicular fluid has a potent inhibitory effect on E_2 production in PCOS (33, 34). This follicular fluid-derived inhibitor decreases aromatase activity by suppressing the P450 aromatase mRNA expression in follicles of PCOS patients (35). Because AMH serum concentrations do correlate with serum levels of T, AD, and SHBG and only weakly with E_2 concentrations, it might be speculated that AMH might constitute this follicular fluid-derived inhibitory factor. Indeed, exogenous AMH did inhibit the biosynthesis of aromatase in cultured rat granulosa cells (36). Moreover, in PCOS women an inverse relationship between E_2 and AMH serum levels has been previously established (20).

A surprising finding constitutes the difference in relative decline in AMH serum levels with increasing age between normal controls and WHO 2 patients, suggesting that the latter group might reach menopause later in life. Because

AMH levels correlate with the number of early antral follicles, which might in turn represent the size of the resting pool of follicles, AMH may constitute a marker for ovarian aging (9, 13). Hence, increased intraovarian AMH production in PCOs may slow down the process of primordial follicle recruitment and thus retard depletion of the primordial follicle pool. Although it has been reported that cycle irregularities and hormonal profiles improve with increasing age (37–39), data regarding the age of menopause in these women are lacking. However, menopausal age in these women is difficult to establish because most of them will regulate their cycles up to advanced age using oral contraceptive pills. Whether AMH can be used as a reliable marker in PCOS should be further substantiated. Moreover, the challenging concept of retarded ovarian aging in PCOS needs further confirmation by properly designed longitudinal follow-up studies.

In conclusion, serum AMH concentrations are elevated in WHO 2 women, which appears to be related to the increased number of small preantral and early antral follicles, especially in those patients exhibiting PCOs. Because AMH concentrations correlated well with other clinical, endocrine, and ultrasound parameters indicative of ovarian dysfunction in these patients, AMH may constitute a novel marker for the extent of the disease. Elevated AMH serum levels in WHO 2 and especially PCOS patients might indicate an increased ovarian reserve.

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