ORIGINAL ARTICLE: REPRODUCTIVE ENDOCRINOLOGY

Antimüllerian hormone: correlation with age and androgenic and metabolic factors in women from birth to postmenopause

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Objective: To study the age-specific distribution of antimüllerian hormone (AMH) and describe the association of AMH with androgenic and metabolic profiles at different ages.
Design: Cross-sectional study.
Setting: University hospital.
Patient(s): A total of 6,763 Chinese women from birth to menopause.
Intervention(s): None.
Main Outcome Measure(s): Anthropometric parameters (height, weight, and blood pressure), and levels of AMH and testosterone, glucose metabolism, and lipid profiles.
Result(s): According to the level of AMH, four age phases were established: childhood (0–10 years), adolescence (11–18 years), reproductive age (19–50 years), and advanced age ($\geq$51 years). During childhood and adolescence, AMH levels increased, reaching a peak at 18 years. A decline occurred thereafter during the reproductive-age period until the age of 50 years, and it remained at a low level above 0 onward. We found that AMH was negatively correlated with testosterone in childhood ($r = -0.25$), but was positively correlated with testosterone and the free androgen index in adolescence ($r = 0.30$; $r = 0.26$, respectively) as well as during the reproductive phases ($r = 0.28$; $r = 0.31$, respectively). No correlation was observed between AMH and body mass index, fasting blood glucose, fasting insulin, the homeostasis model assessment, total cholesterol, triglycerides, low-density lipoprotein, or high-density lipoprotein at any phase.
Conclusion(s): From birth to 18 years, AMH increases, then it declines thereafter, indicating changes of ovarian maintenance. A positive relationship between androgenic profiles and AMH during adolescence and reproductive years implies a synchronism between androgens and ovarian reserve. (Fertil Steril® 2015;■: ■–■. ©2015 by American Society for Reproductive Medicine.)
Key Words: Age, AMH, metabolism, testosterone

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Antimüllerian hormone (AMH) in females is crucial for recruitment and selection of follicle development (1), and it is a promising biochemical marker for ovarian function. Interest has increased in the role of AMH in assessing acyclic ovarian activity (2), evaluating follicular response (1), and predicting the age of menopause (3). The age-dependent model of serum AMH was first generated by Kelsey et al. (4), and the correlation with the nongrowing follicle pool has been well-described using data extracted from published studies. Later, Lie Fong et al. (5) reported an age-specific distribution in Caucasian women from ages 0 to 50 years. However, in view of ethnic variations, additional investigation into different populations and covering childhood, adolescence, and the reproductive years would be helpful for clinical AMH application.

Testosterone is one of the most important ovarian hormones participating in folliculogenesis (6). A positive correlation between AMH and testosterone has been reported, but controversy persists (7–9). A metabolic disturbance will impact female fertility (8), and obesity, elevated blood glucose, and hyperlipidemia occur more frequently in women with increased serum concentrations of follicle-stimulating hormone (10–13). Thus, the relationship between AMH and metabolism is intriguing. The adverse correlation of fasting glucose, fasting insulin, the homeostasis model assessment of insulin resistance (HOMA-IR), and low-density lipoprotein with AMH has been described (14, 15), but it is inconsistent with the data from Anderson et al. (16). We explored the pattern of AMH during the female life span from birth to postmenopause in the largest Chinese study population to date to clarify the association of AMH with androgen and metabolic profiles.

MATERIALS AND METHODS

Participants

A total of 6,763 women from ages 0 through 64 years old (mean age of 26.93 ± 10.86 years) were recruited for our cross-sectional design. The distribution of the age-specific sample size is presented in Supplemental Table 1 (available online). Children aged of 0–14 years (n = 852) were recruited from March to September 2014 from a pediatric clinic where they were being treated for injuries, and all the samples comprised surplus blood remaining from routine examinations. After the written informed consent had been signed by the parents, the samples were obtained and stored at −80°C in advance for use in testing AMH levels. The adolescents (15–20 years, n = 671) were enrolled in the study from Jinan Nursing Academy of Shandong Province, People's Republic of China, where they underwent the physical examination. The reproductive-aged women (21–44 years, n = 5,037) were patients undergoing treatment for tubal obstruction or male factor infertility diagnosed at the Center for Reproductive Medicine, Shandong University, from January 2013 to January 2014. Of the latter women, 196 (3.7%) of 5,037 reported irregular menses. Women older than 45 years (n = 203) were recruited from the Center for Health Examination in the same hospital. Women who had had previous ovarian surgery or who had been exposed to chemotherapy or radiotherapy were excluded. All women at reproductive age were nonpregnant and had had no treatments with hormones, oral contraceptives, or other medications for at least 3 months before the study.

Written informed consent about the objective of the study, the blood sample collected, and other detailed tests was obtained from all participants or from the parents of the children and adolescents. All the results of the tests were returned to the participants individually. The study was approved by the institutional review board of Reproductive Medicine of Shandong University.

Measurements

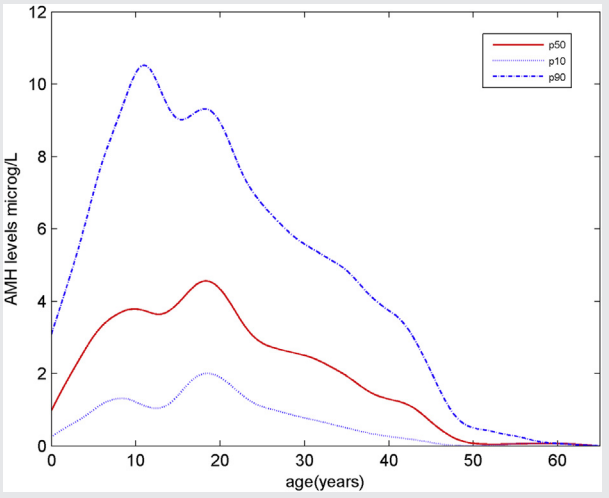
Blood was sampled for AMH, testosterone, and sex hormone-binding globulin using an enzyme-linked immunosorbent assay (for AMH; Ansh Labs), a chemiluminescence immunoassay, and an enzyme-linked immunosorbent assay (for testosterone and sex hormone-binding globulin, respectively; Roche Diagnostics), respectively. Samples with an AMH level of 0 mg/L or exceeding 18 mg/L were considered to be suspicious and were retested on two separate days (n = 51) with an intra-assay and interassay coefficient of variation <10%. The free androgen index was calculated as follows: Testosterone (nmol/L) × 100/Sex hormone-binding globulin (nmol/L). The serum samples were initially separated and routinely stored at −80°C until assayed. Serum AMH levels below 0.08 mg/L (n = 178) were retested using the picoAMH enzyme-linked immunosorbent assay (for AMH: Ansh Labs). In women over 21 years (n = 5,240), blood samples after 8 hours of fasting were obtained for measurement of metabolic parameters. Fasting glucose and fasting insulin were measured using the oxidase method and chemiluminescence immunoassays. We derived HOMA-IR by the following calculation: Fasting glucose (mmol/L) × Fasting insulin (mIU/mL)/22.5. Serum total cholesterol, triglycerides, low-density lipoprotein, and high-density lipoprotein were evaluated in fasting blood samples using the precipitation and enzymatic methods.

All patients, except for the children aged 0–14 years recruited from pediatric clinics, were subjected to anthropometric data (including height and weight) and had their medical history (including menstrual cycle, surgery, and systemic disease) recorded. Body mass index (BMI) was calculated using following formula: Weight (kg)/Height^2 (m^2).

Statistics

Data analysis was performed using MATLAB 2013b (MathWorks). Age-specific distribution curves were calculated from a nonparametric regression model using a smooth spline fitted on log-transformed AMH values. A piecewise linear function was calculated from the fitted curve to demonstrate the periodic variation of AMH with age. The age with the maximum level of AMH was determined by bootstrapping 5,000 times. Bivariate correlations were performed between AMH and age, testosterone, and the free androgen index, respectively, in each subgroup. Correlation analyses were also performed between AMH and BMI as well as other

FIGURE 1



Levels of serum antimüllerian hormone (AMH) from neonatal to postmenopause. Reference lines refer to the 10th, 50th, and 90th percentiles of serum AMH value.

Cui. AMH, age, androgen, and metabolism. Fertil Steril 2015.

metabolic parameters in samples drawn after fasting. Bonferroni modification was used, and $P<.005$ (0.05/10) was considered statistically significant.

RESULTS

Age-specific distribution of serum AMH

The median, quartile, mean, and standard deviation (SD) of serum AMH at each age are shown in Supplemental Table 1. In the total cohort, the AMH level was inversely correlated with age, with a coefficient of −0.34 ($P<.01$). The fitted curve shows its pattern across the life span (Fig. 1). Using a piecewise linear function, we obtained four distinct phases (Fig. 2). The mean level and reference range of AMH in each subgroup are shown in Table 1. From birth to 10 years of age, a sharp ongoing rise occurred with an increasingly wide reference range. The level of AMH positively correlated with age during this phase ($r = 0.48$, $P<.01$). A slight rise with fluctuations occurred between the ages of 10 and 18 years. The correlation was statistically significant although to a lesser extent ($r = 0.18$, $P<.01$). We found a maximum AMH value of 4.56 mg/L at 18 years (95% confidence interval, 11.0–18.9); thereafter, a statistically significant decrease occurred to 50 years of age, also seen in the reference range. We demonstrated a negative correlation between AMH and age during this phase ($r = -0.41$, $P<.01$). From the age of 50 years onward, AMH remained at a very low level, around 0 mg/L; no correlation could be calculated.

Correlation between AMH and Androgen

The correlation between AMH and androgen is shown in Table 2. A negative correlation of AMH with testosterone was found for the ages 0–10 years ($r = -0.25$, $P<.005$). A positive correlation was found for the age ranges 11–18 years and 19–50 years in both testosterone ($r = 0.30$, $P<.005$, and $r = 0.28$, $P<.005$, respectively) and the free androgen index ($r = 0.26$, $P<.005$, and $r = 0.31$, $P<.005$, respectively).

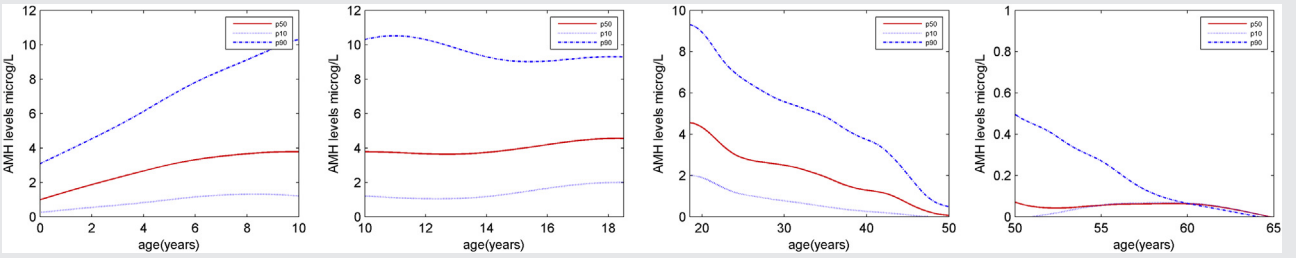
Correlation between AMH and Metabolic Parameters

We measured BMI and other metabolic parameters in women aged 21–64 years. A negative correlation was found between AMH and BMI ($r = -0.18$, $P<.01$) and fasting glucose ($r = -0.08$, $P<.01$) during the 21–50 years age range, although with limited clinical significance. No correlation was found between AMH and fasting insulin, HOMA-IR, total cholesterol, triglycerides, low-density lipoprotein, or high-density lipoprotein (data not shown).

DISCUSSION

This cross-sectional study of a large cohort of Chinese women from infancy to postmenopause presents a trend nomogram of serum AMH. Four specific phases related to AMH were demonstrated: childhood (0–10 years), adolescence

FIGURE 2



Distribution of antimüllerian hormone (AMH) at different age phases. Reference lines refer to the 10th, 50th, and 90th percentiles of serum AMH value. Four phases were divided as childhood (0–10 years, *first panel*), adolescence (11–18 years, *second panel*), reproductive age (19–50 years, *third panel*), and advanced age (51 years and older, *last panel*).

Cui. AMH, age, androgen, and metabolism. Fertil Steril 2015.

TABLE 1

Antimüllerian hormone (AMH) values at four age phases.

Age phase (y)	No. of women	AMH (mg/L)[a]	Reference range (mg/L)[b]
0–10	739	3.09 ± 2.91	0.39–6.67
11–18	471	5.02 ± 3.35	1.52–9.41
19–50	5,500	2.95 ± 2.50	0.54–5.93
≥51	53	0.22 ± 0.36	0–0.65

[a] Mean ± standard deviation.
[b] Reference range was presented as P10–P90.

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(11–18 years), reproductive age (19–50 years), and advanced age (51 years and older).

During childhood, we found that AMH levels rose rapidly with increasing age. It was formerly believed that AMH was undetectable at birth and increased to the ages of 2–4 years, remaining stable thereafter until adulthood (17, 18). In contrast, our data indicate that the concentration of AMH at birth is 1.66 mg/L, supporting the premise that AMH is first secreted by fetal granulosa cells at 36 weeks' gestation (19). The continuous rise of AMH after birth persists to about 10 years, and thus appears to parallel the initiation of follicular growth.

Adolescence manifested with the highest level of AMH across the whole life span; levels of approximately 5 mg/L were maintained during this phase despite obvious fluctuations. A poor correlation was found between AMH and age during this phase, in accordance with prior longitudinal follow-up studies (20, 21). A declination in the level of AMH was observed from age 12 to 14. A similar fall from 8 years to 12 years was described by Kelsey et al. (4). As this fall coincides with the initial increase of gonadotropin concentration during early puberty (22), it may reflect the change in the proportion of follicles at different stages. It is interesting that different peak ages of AMH level have been reported: Fong et al. reported the peak age at 15.8 years, whereas Kelsey et al. reported it at 24.5 years (4). Our data showed the peak occurring at 18 years with a decline soon afterward. The difference could be explained by varying ethnicity, environmental factors, or nutritional status. A high level of AMH during adolescence may serve as the first predictor of natural fertility and reproductive life span (2).

After the age of 18 years, the AMH level statistically significantly declines with age until 50 years, which is consistent with previous studies (4, 5, 23). This pattern of age-dependent decrease indicates the pivotal effect of age on the ovarian reserve.

Androgens are regarded as one factor affecting the ovarian reserve, so AMH levels are believed to be associated with them. It has been demonstrated that high-doses of testosterone decrease the production of AMH in vitro (7). However, Ikeda et al. (9) observed that the administration of androgens increased AMH secretion in a rat model. We found a positive correlation between AMH levels and androgenic parameters during adolescence and the reproductive period, indicating a synchronous synthesis of AMH by granulosa cells and androgen by theca cells in young women.

We found no clinically significant correlation with between AMH and metabolic parameters. This is consistent with previous observations about lipid profiles in women of reproductive age (14, 15). Nor did we confirm an association between AMH and BMI. Although statistical significance was found in the subgroup of 21–50 years, little clinical significance could be drawn, given the very low correlation coefficient between AMH and BMI. As reported, caution should be exercised for specific populations such as patients with polycystic ovary syndrome (PCOS), diminished ovarian reserve, or obesity (24–28). Controversy also exists regarding the correlation of AMH with glucose metabolism. It has been reported that the serum AMH level decreases with an increase in fasting glucose and fasting insulin in women of reproductive age (29) but that the pattern is different in women with PCOS (30). However, in our study, no statistically significant correlation was found in women over 21 years of age, so further investigation in young women is needed.

The strengths of our study include the largest sample size collected to date, covering the entire life span, with endocrine hormone and metabolic parameter measurements. All samples were handled by the same protocol for preparation, storage, and measurement in a single laboratory using one particular AMH assay. We also validated the Ansh Labs picoAMH assay for clinical and research in newborn and postmenopausal females. However, there are several limitations. First, the reproductive-aged women were patients in a reproductive clinic. Although we limited the causes of infertility to either tubal factor or male factor, a potential for selection bias exists. Thus, the findings cannot be exactly extrapolated to a fertile population. Second, the sample size in certain age groups was relatively small, especially the

TABLE 2

Correlation of antimüllerian hormone with androgenic parameters during each age phase.

	0–10 y		11–18 y		19–50 y		≥51 y	
Androgenic parameter	***r***	***P* value**	***r***	***P* value**	***r***	***P* value**	***r***	***P* value**
Testosterone	−0.25[a]	<.005[a]	0.30[a]	<.005[a]	0.28[a]	<.005[a]	0.21	NS
Free androgen index	−0.11	NS	0.26[a]	<.005[a]	0.31[a]	<.005[a]	0.06	NS

Note: NS = not statistically significant.
[a] Statistically significant. Bonferroni modification was used, and $P<.005$ (0.05/10) was considered statistically significant.

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prepuberty population. Finally, measurement of testosterone with enzyme-linked immunosorbent assays is less reliable than with liquid chromatography–mass spectrometry, which may have impacted the correlation analysis to some extent.

CONCLUSION

Our study, featuring the largest well-characterized population from the neonatal to postmenopause periods to date, provides a comprehensive understanding of the relationship between AMH and age. We propose four age phases: childhood (0–10 years), adolescence (11–18 years), reproductive age (19–50 years), and advanced age (51 years and older), with elevated AMH levels in the first two phases and diminished levels during reproductive age. This will allow more accurate assessment of fertility potential for individual woman at different ages. In addition, the relationship between androgen and AMH during the adolescent and reproductive ages implies synchronicity between androgen and ovarian reserve. In contrast, the metabolic profiles had no correlation with ovarian reserve in any age subgroup.

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SUPPLEMENTAL TABLE 1

Number of participants and antimüllerian hormone (mg/L) levels at each year interval.

Age (y)	No.	Median	Q25	Q75	Mean	1 SD
0	110	0.72	0.10	1.68	1.30	1.94
1	124	1.73	1.11	2.60	2.10	1.96
2	89	1.97	1.13	3.24	2.39	1.64
3	50	1.92	0.71	4.00	2.54	2.33
4	70	2.48	1.18	4.11	2.85	2.10
5	55	3.13	1.59	5.25	3.88	3.24
6	57	3.84	2.32	6.24	4.74	3.22
7	50	3.09	1.85	5.88	4.11	3.32
8	30	3.48	1.75	5.51	3.99	2.73
9	45	4.04	2.77	6.83	4.98	3.03
10	59	3.89	1.96	7.90	5.21	4.19
11	31	4.30	2.31	6.28	5.32	4.58
12	20	3.39	1.71	8.24	5.28	4.41
13	40	3.03	1.74	4.50	4.02	3.86
14	22	3.54	1.55	5.38	3.76	2.82
15	68	3.77	2.53	6.36	4.64	3.30
16	91	4.21	2.85	6.46	4.91	2.84
17	101	4.49	3.19	6.68	5.22	2.75
18	98	5.12	3.15	7.59	5.74	3.48
19	167	4.67	3.12	7.03	5.50	3.43
20	146	4.38	3.12	6.28	5.18	3.25
21	94	4.41	2.78	6.50	4.90	2.94
22	71	3.41	2.17	5.21	4.09	3.10
23	127	2.87	1.76	4.78	3.54	2.50
24	182	2.75	1.70	4.61	3.52	2.62
25	320	2.81	1.87	4.20	3.37	2.37
26	356	2.84	1.93	4.51	3.46	2.20
27	344	2.73	1.69	4.30	3.45	2.75
28	361	2.73	1.55	4.20	3.30	2.64
29	300	2.39	1.40	3.85	2.88	2.00
30	371	2.54	1.55	3.87	3.01	2.18
31	398	2.59	1.45	4.05	3.06	2.29
32	340	2.38	1.39	3.56	2.83	2.16
33	313	1.97	1.12	3.20	2.42	1.92
34	241	2.04	1.16	3.44	2.60	2.20
35	215	2.25	1.17	3.80	2.74	2.25
36	166	1.79	0.98	2.87	2.37	2.17
37	172	1.42	0.69	2.48	1.76	1.44
38	133	1.34	0.61	2.49	1.84	1.82
39	119	1.30	0.75	2.23	1.73	1.74
40	115	1.17	0.54	2.11	1.74	2.42
41	107	1.29	0.72	2.48	1.83	1.85
42	84	1.26	0.46	2.22	1.78	2.04
43	48	1.34	0.43	1.81	1.50	1.52
44	60	0.95	0.50	1.70	1.29	1.18
45	32	0.45	0.14	1.01	0.77	0.85
46	28	0.41	0.13	0.95	0.61	0.61
47	16	0.35	0.07	0.65	0.39	0.36
48	22	0.03	0.00	0.18	0.10	0.15
49	28	0.12	0.01	0.30	0.28	0.52
50	24	0.09	0.01	0.18	0.15	0.19
≥51	53	0.08	0.00	0.28	0.22	0.36

Note: Q25 = 25th percentile; Q75 = 75th percentile; SD = standard deviation.

Cui. AMH, age, androgen, and metabolism. Fertil Steril 2015.