

Variations and Age-Specific Reference Ranges of Anti-Müllerian Hormone in Healthy Chinese Women of Reproductive and Perimenopausal Age: a Prospective Nationwide-population based Prospective Cross-sectional Study

Categories: Reproductive medicine/assisted reproduction

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BACKGROUND

What is known already:

- AMH is a dimeric glycoprotein that undergoes initial follicular recruitment. As a crucial biomarker evaluating ovarian reserve functions^[1], serum AMH has been actively measured to predict the response to ovarian stimulation and pregnancy outcomes of *in vitro fertilization* (IVF)^[2-4].
- Previous studies showed that age and ethnicity could independently affect the variation of serum AMH levels: AMH in adult Chinese women was substantially lower than that in their European counterparts from age 25 onwards^[5].
- AMH could rapidly decrees at the end of fertility (40-50 years) and become undetectable approximately five years before the final menstrual period^[6], endowing its potential to evaluate perimenopause fertility and also aid in the understanding of fertility transition during perimenopause^[7].

Objective:

- To establish age-specific AMH reference ranges for Chinese women of reproductive and perimenopausal age.
- To investigate the variation of AMH during the fast fertility-declining ages >40 years.

METHODS

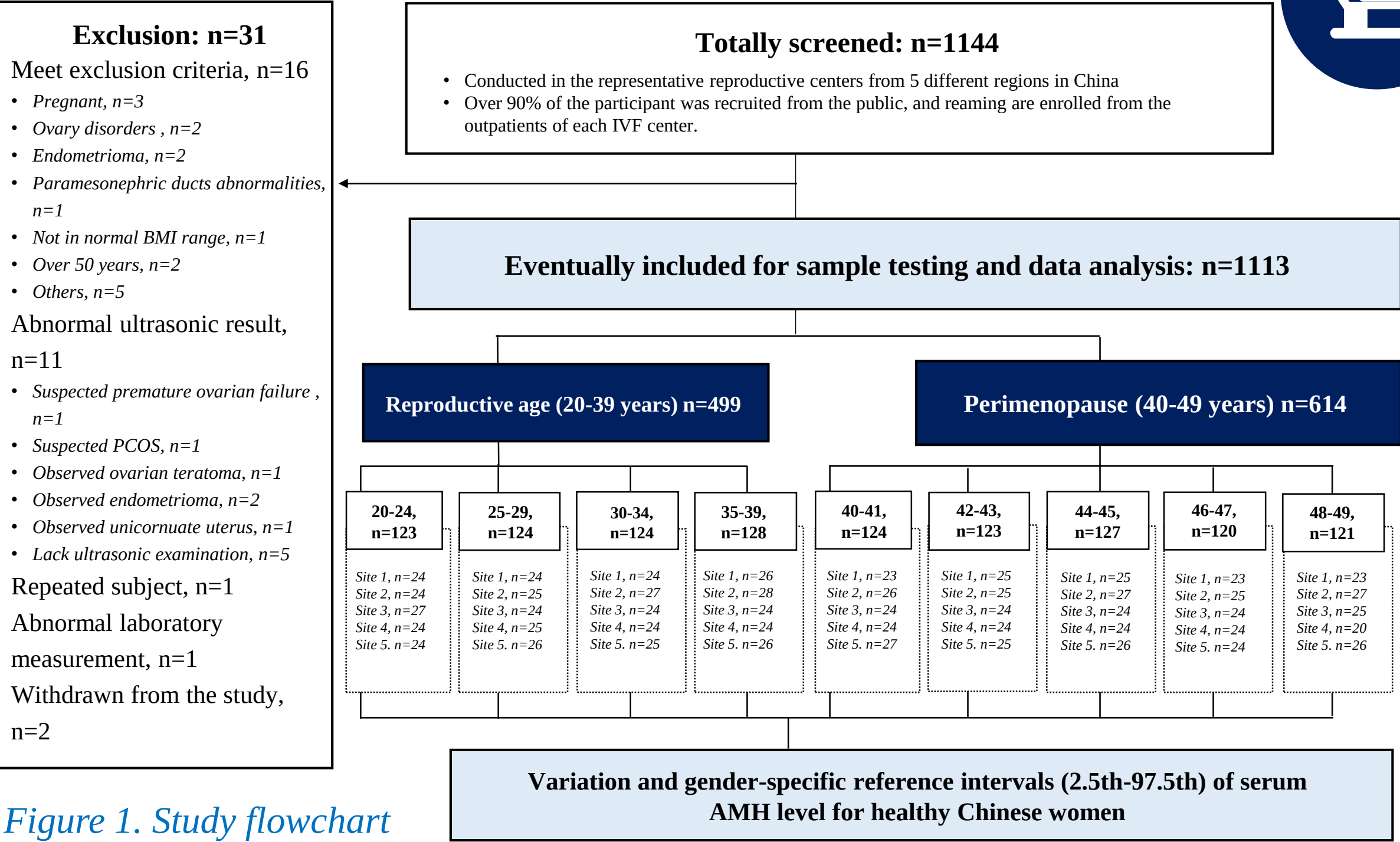


Figure 1. Study flowchart

- This prospective cross-sectional multicenter study was started in May 2022 and finished in February 2023.
- This study was designed to enroll ≥ 1080 subjects (20-49 years) from five reproductive centers: central, eastern, western, northern, and southern, with ≥ 480 subjects of reproductive age (20-39 years) and ≥ 600 in perimenopause (40-49 years)), and the two age groups are composed of 4 and 5 subgroups (n ≥ 120) with an interval of 2 and 5 years, respectively.
- Serum AMH level was measured using the Elecsys® AMH Plus immunoassay on Cobas® e601 or e602 (Roche Diagnostics GmbH).

RESULTS

Demographics and clinical characteristics of the study population

- In this study, 1144 subjects were screened and 1113 healthy Chinese women were enrolled for investigation, with 499 of reproductive age (44.9%) and 614 of perimenopausal age (55.1%). Over 90% of the subjects were recruited from the public. Most of the subjects are Han ethnicity (98.7%) and were recruited from the publics (>90%). For each participant, their BMI, weight, height, menstrual cycle, length of menstruation were fully recorded (100%), with the mean (SD) of 21.9 (1.9), 160.6 (5.2) cm, 55.4 (6.1) kilogram, 29.0 (2.1) days, and 5.5 (1.2) days.
- Clinical laboratory results:** the serum AMH of each subjects was measured, with the mean (SD) of 1.8 (2.0) ng/ml. Subjects have female sex hormone results recorded at the 2nd-5th day of menstruation were directly enrolled from the outpatient of each IVF centers (<10%), including 99 (8.8%) E2, 93 (8.3%) FSH, 100 (9.0%) P, 58 (5.2%) PRL, 57 (5.1%) T, and 98 (8.8%) LH results. Their respective mean (SD) value is 48.5 (30.3) pg/mL, 7.5 (3.3) mIU/mL, 0.8 (2.5) ng/mL, 18.7 (8.2) ng/mL, 10.1 (12.1) ng/dL, and 5.6 (2.4) mIU/mL.

Establishing Age-Specific Reference Ranges of AMH for Healthy Chinese Women

Table 1. Age-specific reference ranges of AMH in healthy Chinese women of different age groups.

	Reproductive age / years					Perimenopausal age /years				
	20-24	25-29	30-34	35-39	40-41	42-43	44-45	46-47	48-49	
Mean (SD), ng/mL	3.9 (2.3)	3.7 (2.1)	3.0 (1.9)	2.2 (1.4)	1.6 (2.1)	1.0 (1.1)	0.6 (0.7)	0.3 (0.5)	0.2 (0.3)	
Percentiles										
2.5th	0.87	0.64	0.61	0.28	0.12	0.01	0.01	0.01	0.01	
5th	1.17	0.98	0.77	0.41	0.21	0.01	0.01	0.01	0.01	
10th	1.65	1.40	0.95	0.63	0.30	0.13	0.01	0.01	0.01	
25th	2.43	2.14	1.56	1.08	0.66	0.33	0.12	0.01	0.01	
50th	3.44	3.50	2.73	1.84	1.42	0.68	0.38	0.12	0.05	
75th	4.85	4.84	3.69	3.05	2.27	1.38	0.90	0.35	0.18	
90th	6.71	6.70	5.75	4.05	3.05	2.51	1.38	0.65	0.49	
95th	8.02	7.12	6.92	4.79	3.64	2.89	1.99	1.14	0.72	
97.5th	9.84	8.20	7.76	5.59	4.62	4.10	2.64	1.76	1.08	

- The ranges from 2.5th to 97.5th percentile should be recommended as the reference intervals of AMH in clinical practices in China.
- The upper limit of most AMH reference ranges established in this study are lower than the relative ranges for European women that were established based on a Roche study included 887 health subjects (RD001727). This observation may further supported the reported difference in AMH between ethnicities^[8].

Decline in serum AMH level with age

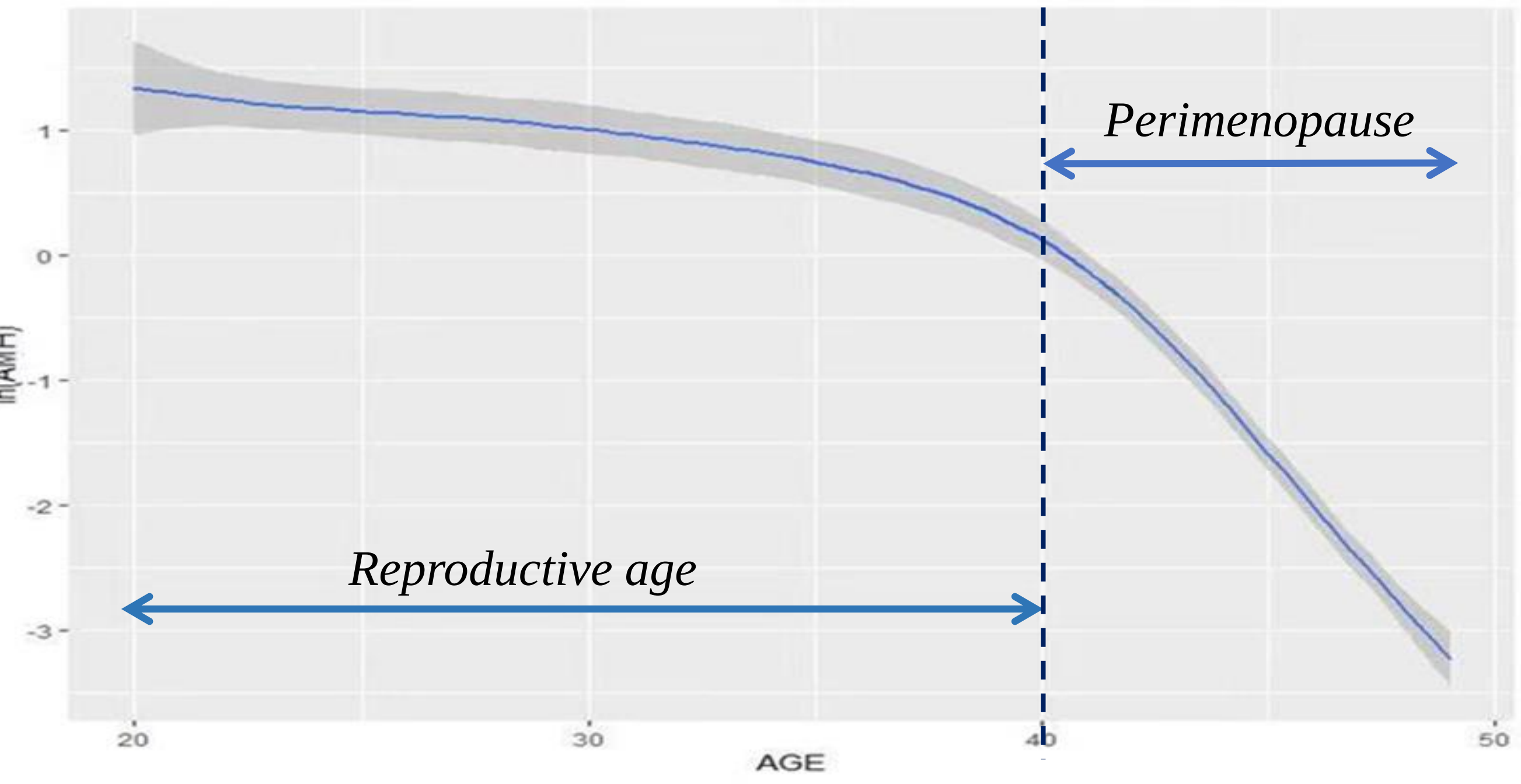


Figure 2. Variations of serum AMH level in healthy Chinese Women ranges from Reproductive Age to Perimenopause

- Serum AMH level consistently decrease after 20 years. Around the starting of perimenopause (ca. 40 years), the decline of AMH becomes more precipitous (Figure 2 above).
- Both the trend of AMH level for women of 20-49 and the accelerated decline around 40 years observed in this study are similar to the previous studies conducted in China^[9-11].

Associations of AMH with Various Demographic and Clinical Variables

- Univariable regression:** age, BMI, and FSH are negatively correlated with AMH (all P<0.001). In the contrary, menstrual cycle, length of menstruation, and T are positively correlated with AMH (all P<0.05).
- Multivariable regressions**
 - Age is an independent variable that negatively associates with AMH when adjusted by any female sex hormone (all P<0.05). For length of menstrual cycle and FSH, their respective association AMH is also independent (positive and negative, all P<0.05).
 - The variations of AMH and the female hormones on age fitted by multivariable regressions were plotted and demonstrated in Figure 3a. A negative linear association independent of age and BMI was determined between AMH and FSH; The association between AMH and T is positive linearly affected by BMI.
- No linear correlation between LH and AMH was determined, due to a interaction effect of LH and age on AMH (Figure 3b). To be more specific, the negative correlation between FSH and AMH existed among the whole age range of this study, while the negative association between LH and AMH only exists in perimenopause.

CONCLUSIONS

This nationwide population-based study established the age-specific AMH reference ranges for Chinese women of reproductive and premenopausal age (20-49 years).

Serum AMH level consistently decrease after 20 years. Around the starting of perimenopause (ca. 40 years), this decrease becomes more precipitous

As the fast decline of AMH during perimenopause was determined, we hope the comprehensive 2-year ranges built for women of this age could be valuable in evaluating premenopausal fertility transformation in clinical practice.

Age, length of menstrual cycle, and FSH are independently associate with AMH

DISCLOSURES

Ethics approval and consent to participate: This study is strictly in accordance with the Declaration of Helsinki and was approved by the ethics committees of each site, All participants have signed the informed consent forms before the enrollment.

Competing interests: Cun-Ying Pu is an employee of Roche Diagnostics (Shanghai) Limited. Other authors declared no conflict of interest.

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