Editorial

Ann Lab Med 2022;42:617-618
https://doi.org/10.3343/alm.2022.42.6.617
ISSN 2234-3806 • eISSN 2234-3814

ANNALS OF LABORATORY MEDICINE

Haeil Park, M.D., Ph.D.

Department of Laboratory Medicine, Bucheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

Age-specific Reference Intervals for Anti-Müllerian Hormone

Readers who are considering having their ovarian reserve tested will be interested in the study by Ji, *et al.* [1] in this issue of *Annals of Laboratory Medicine.* Anti-Müllerian hormone (AMH) or Müllerian-inhibiting substance is a glycoprotein of the transforming growth factor-β superfamily [2]. Following secretion by Sertoli cells in a male fetus, AMH induces the regression of the Müllerian ducts during development [3]. In women, AMH is produced by granulosa cells during early follicle development. As its level correlates with the number of antral follicles, it may be used as a marker of ovarian reserve [4]. For clinical judgment of ovarian function based on serum AMH levels, a reference interval for comparison is required. The current AMH reference interval was established using ELISA [5]. Recently, automated assays have been developed, and these yield lower AMH levels than ELISA [6, 7]. Therefore, it is necessary to establish a reference interval suitable for the new test method [8-10].

As the serum AMH level decreases with age, reference intervals should be determined according to narrow age bins. Therefore, establishing reference intervals is more cumbersome for AMH than for other analytes. Ji, *et al.* [1] calculated 5-year age-specific reference intervals, with all age bins comprising more than 120 reference individuals. They measured AMH levels in serum samples collected in the Korea National Health and Nutrition Examination Survey (KNHANES), a nationwide population-based study [11, 12], and cryopreserved in the National Biobank. In total, 1,450 participants in KNHANES between 2013 and 2016 were enrolled. Had the study not used KNHANES data, procuring such a large number of participants to calculate reference intervals would have been challenging. A previous study that established a reference interval for an automated assay had potential for selection bias because it included women who visited an infertility center [13]. The strategy used by Ji, *et al.* [1] of including participants in a population-representative study likely is more reliable.

Given that KNHANES targets the general population, most examinees are likely to be healthy. Healthy participants for reference were selected by applying inclusion criteria. The authors carefully considered factors that may potentially affect the reference AMH levels by measuring serum progesterone levels and performing bone morphogenetic protein-15 genetic testing [1]. The Roche assay used by the authors has a relatively large market share among automated assays [14]. Therefore, many researchers will be able to reference the study results.

The greatest significance of this study is that the authors considered ethnic differences in serum AMH levels [9, 15, 16]. The reference interval mentioned in the package insert of the AMH assay reagent may not be suitable for the target population. This is evident from the reference interval calculated by the authors, which was wider than that mentioned in the package insert, exceeding the limits at both ends of the range. The median serum AMH level in the 25–34-year-old Korean population tended to be slightly higher than that in the Caucasian population [1].

More extensive use of KNHANES participant data or samples in studies to establish reference intervals for analytes would be

beneficial; however, it has some limitations. First, depending on the analyte, the information required to identify reference individuals may be lacking. Second, for an analyte that does not have a premeasured value, it may be impossible to measure it because of the limited amount of sample stored. In the study by Ji, *et al.* [1], the AMH levels of 21 participants could not be measured because of insufficient sample volumes. A multicenter study can be a robust alternative to reference interval studies [17].

AUTHOR CONTRIBUTIONS

Park H accepts responsibility for the content of this manuscript and has approved its submission.

CONFLICTS OF INTEREST

No potential conflicts of interest relevant to this paper were reported.

REFERENCES

1. Ji M, Kim K, Kim H, Lee W, Yun Y, Chun S. Age group-specific reference intervals for the Elecsys anti-Müllerian hormone assay in healthy Korean women: a nationwide population-based study. Ann Lab Med 2022;42:621-31.
2. Cate RL, Mattaliano RJ, Hession C, Tizard R, Farber NM, Cheung A, et al. Isolation of the bovine and human genes for Müllerian inhibiting substance and expression of the human gene in animal cells. Cell 1986;45:685-98.
3. Lee MM and Donahoe PK. Mullerian inhibiting substance: a gonadal hormone with multiple functions. Endocr Rev 1993;14:152-64.
4. Broer SL, Broekmans FJ, Laven JS, Fauser BC. Anti-Müllerian hormone: ovarian reserve testing and its potential clinical implications. Hum Reprod Update 2014;20:688-701.
5. Lee JY, Ahn S, Lee JR, Jee BC, Kim CH, Seo S, et al. Reference values for the revised anti-Müllerian hormone generation II assay: infertile population-based study. J Korean Med Sci 2017;32:825-9.
6. Nelson SM, Pastuszek E, Kloss G, Malinowska I, Liss J, Lukaszuk A, et al. Two new automated, compared with two enzyme-linked immunosorbent, antimüllerian hormone assays. Fertil Steril 2015;104:1016-21.e6.
7. van Helden J and Weiskirchen R. Performance of the two new fully automated anti-Müllerian hormone immunoassays compared with the clinical standard assay. Hum Reprod 2015;30:1918-26.
8. Cheng X, Zhang Q, Liu M, Li S, Tao Z, Ichihara K, et al. Establishing age-specific reference intervals for anti-Müllerian hormone in adult Chinese women based on a multicenter population. Clin Chim Acta 2017;474:70-5.
9. El-Attar EA, Hosny TA, Ichihara K, Bedair RN, Tork ASE. Nomogram of age-specific anti-Müllerian hormone levels in healthy Egyptian females. PLoS One 2021;16:e0254858.
10. Song J, Park Y, Cho HW, Lee SG, Kim S, Lim JB. Age-group-specific reference intervals for anti-Müllerian hormone and its diagnostic performance for polycystic ovary syndrome in a Korean population. J Clin Lab Anal 2021;35:e23861.
11. Kim Y. The Korea National Health and Nutrition Examination Survey (KNHANES): current status and challenges. Epidemiol Health 2014;36:e2014002.
12. Kweon S, Kim Y, Jang MJ, Kim Y, Kim K, Choi S, et al. Data resource profile: the Korea National Health and Nutrition Examination Survey (KNHANES). Int J Epidemiol 2014;43:69-77.
13. Han A, Suh B, Yi G, Lee YJ, Kim SE. Comparison of the automated fluorescent immunoassay system with Roche Elecsys and Beckman Coulter Access 2 assays for anti-Müllerian hormone measurement. Ann Lab Med 2022;42:47-53.
14. Kim S, Lee K, Park HD, Lee YW, Chun S, Min WK. Schemes and performance evaluation criteria of Korean Association of External Quality Assessment (KEQAS) for improving laboratory testing. Ann Lab Med 2021;41:230-9.
15. Bleil ME, Gregorich SE, Adler NE, Sternfeld B, Rosen MP, Cedars MI. Race/ethnic disparities in reproductive age: an examination of ovarian reserve estimates across four race/ethnic groups of healthy, regularly cycling women. Fertil Steril 2014;101:199-207.
16. Nelson SM, Aijun S, Ling Q, Tengda X, Wei X, Yan D, et al. Ethnic discordance in serum anti-Müllerian hormone in healthy women: a population study from China and Europe. Reprod Biomed Online 2020;40:461-7.
17. Sung JY, Seo JD, Ko DH, Park MJ, Hwang SM, Oh S, et al. Establishment of pediatric reference intervals for routine laboratory tests in Korean population: a retrospective multicenter analysis. Ann Lab Med 2021;41:155-70.

Corresponding author: Haeil Park, M.D., Ph.D.
https://orcid.org/0000-0002-1092-0607
Department of Laboratory Medicine, Bucheon St. Mary's Hospital, The Catholic University of Korea, 327 Sosa-ro, Wonmi-gu, Bucheon 14647, Korea
Tel: +82-32-340-2093, Fax: +82-32-340-2219
E-mail: phi@catholic.ac.kr

Key Words: Anti-Müllerian hormone, Reference interval, Immunoassay