Next Steps Toward AMH as a Robust Biomarker for Assessing Ovarian Aging in Individual Women.

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Anti-Müllerian hormone (AMH) is a glycoprotein produced by the gonads and a member of the transforming growth factor superfamily, similar to inhibins. Previously, this hormone was referred to as Müllerian-inhibiting substance, known for its pivotal role in male embryonic sexual differentiation. More recent studies using female AMH knock-out mice convincingly elucidated its crucial role in the recruitment of follicles from the resting primordial pool resulting in premature follicle exhaustion (1).

Initial human studies suggested that AMH could indeed be used as a marker of the remaining functional ovarian reserve (2). The study by de Vet et al was recently elected as 1 of 25 seminal papers by the American Society of Reproductive Medicine, emphasizing the key significance of ovarian aging in current infertility care (2). The key questions remain, however, as to what extent the amount of growth of AMH-producing follicles truly represents the size of the remaining resting primordial follicle pool and whether this is constant across the life course. Direct counting of the number of follicles present in human ovaries is not feasible. A more practical approach would be to assess whether single or repeat measurements of AMH concentrations at a younger age is associated with the age of menopause, a state of terminal follicular depletion, later in life. This would provide indirect proof that the size of the group of developing follicles is indeed a direct representation of the remaining resting follicle pool.

It is well established that both natural and assisted conception pregnancy rates decline significantly with increasing female age (3). However, the 100-fold difference in follicle count that can be observed in 2 women of the same age, which unsurprisingly covers the wide age range of 40 to 60 years of menopause, renders age per se of limited value as a marker of ovarian reserve. To be able to use AMH as a robust biomarker of ovarian aging would be of great clinical significance, but—not surprisingly—life is not that simple.

A recent individual patient data meta-analysis published in this journal involving measurements of AMH at a single time-point in 7 cross-sectional cohorts and a total of 2,596 women of whom 1,077 already experienced menopause concluded that AMH was associated with time to menopause with low precision, and any improvement above age alone was restricted to those women with an early menopause before 45 years (4). It is to be expected that repeated AMH measurements in longitudinal studies, accounting for the individual's trajectory of decline, may improve precision. The analysis of a Dutch population cohort of 2,434 women followed every 5 years for a total of 20 years concluded that knowledge of the individual AMH decline rates did not improve the prediction of menopause for women above the age of 25 years (4). In contrast, the Penn Ovarian Aging Study involving 293 women with 2 measures of AMH over a 14-year follow-up did suggest that the rate of decline was an independent predictor of time to menopause (5). These findings are in accordance with the study by Therani and colleagues (this issue). The authors report a prospective cohort study of 959 reproductive aged women, with follow-up twice after initial screening with an average interval of 6 years between measurements. After a total

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of 14 years follow-up, 529 (55%) reached menopause. The authors concluded that the model's discrimination adequacy, as assessed by C-statistic, increased from 0.70 (95% confidence interval 0.67, 0.71) for a single AMH assessment to 0.78 (95% confidence interval 0.75, 0.80) for repeated measurement; the median difference between actual and predicted age of menopause decreased from –0.48 to –0.21 years, respectively. Whether these opposing findings between studies reflect different populations studied, differences in the frequency of follow-up, or differences in the methodology for ascertainment of AMH concentration remains unclear, but notably none of these studies have confirmed the predictive validity of the derived models in an external population.

AMH is currently being used in clinical practice as a marker for ovarian aging in a great variety of conditions, such as the early diagnosis of premature ovarian insufficiency, assessing the extent of ovarian damage due to chemotherapy or surgery, assessing of chances of spontaneous pregnancy in women with the desire to have children now or later (which may also be relevant for a decision to freeze oocytes for later use), assessment of ovarian responsiveness to stimulation to allow individualization of the extent of ovarian stimulation for in vitro fertilization, and, finally, assessment of chances of pregnancy in "infertile" women of more advanced reproductive age relevant for making decisions about the most appropriate treatment option, which may also include the use of donor oocytes. In addition, AMH is being intensely studied as a potential diagnostic marker of polycystic ovary syndrome to potentially replace the need to assess ovarian morphology by transvaginal ultrasound.

The application of AMH assays to routine clinical practice has been problematic (6). Although robust reproducible automated assays with good technical performance are readily available currently, older, less sensitive manual enzyme-linked immunosorbent assays, known to exhibit substantial variation and require steps to deal with complement interference, are still frequently reported. Even the modern assays do not have equivalent calibration, rendering their interpretation assay-specific. Clinical interpretation is also fraught with difficulty as factors that alter folliculogenesis (such as steroid contraceptive pill use) or ethnic differences may influence AMH concentrations (7). Lastly, for long-term prediction, even mild fluctuations across and between menstrual cycles may impact on accuracy.

In summary, the accurate prediction of age of menopause for a given woman at younger age would be exciting, both in the context of distinct individual variation in the onset of decreased fertility along with the age of menopause related long-term general health risks such as well-being, osteoporosis, breast cancer, and cardiovascular health. Whether predictive potential may improve further by combining AMH concentrations with single nucleotide polymorphism patterns associated with age of menopause warrants further investigation. At present, prior to clinical adoption, clarification of the generalizability of models, including its use in different ethnic populations, and determination of whether measurement at a young enough age with adequate precision to inform reproductive choices is feasible remain critical.

Additional Information

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