

## JAMA Insights

## Diagnosing the Onset of Menopause

Nanette Santoro, MD; Joshua Johnson, PhD

**A 50-year-old woman** with a fibroid uterus and heavy menses presents with 4 months of amenorrhea. She would like to know when she will become menopausal because she wishes to avoid a surgical procedure, but does not feel that she can tolerate many more heavy menstrual periods.

The cessation of ovarian function, termed *menopause*, is an occult event that is only evident after 12 consecutive months of amenorrhea. Longitudinal studies of the 12-month window that defines the final menstrual period (FMP; taken here as defining the onset of menopause) showed that variable estrogen, but no progesterone, production was observed during this time.<sup>1</sup> Most of what is known about the timing of the FMP is based upon observations of menstrual interval tracking among women older than 45 years who had regular menstrual cyclicity before entering the transition. Women who have undergone hysterectomy or endometrial ablation have no bleeding events, precluding the use of menstruation to establish menopause. It is also difficult to establish menopause in women whose FMP occurs unusually early in life or in women with chronically irregular cycles or longstanding amenorrhea.

There are well-validated, menstruation-based criteria for the menopausal transition.<sup>2,3</sup> The early phase of the menopausal transition is entered when a woman with a previously regular cycle experiences irregularity in her intermenstrual interval of 7 days or more. Almost all women experience this at a median age of 47 years.<sup>3</sup> The next menstrual marker, occurring at a median age 49 years, is amenorrhea lasting more than 60 days; this defines the late transition, with a 95% probability that the FMP will occur within 4 years.<sup>4</sup> The

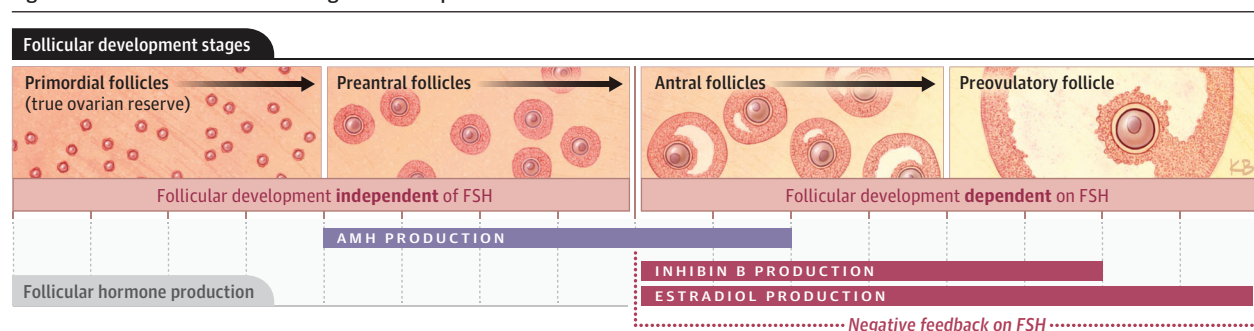
median age of the FMP for US women is 52.5, with a left-skewed distribution, with most women becoming menopausal between ages 47 to 54 years, although sociodemographic factors, such as body mass index and education, and social stressors influence this age distribution.<sup>5</sup> For many women, these markers are sufficient to predict the FMP.

Age at onset of the menopausal transition is predictive of its duration, with women who enter the transition at earlier ages having longer and more symptomatic transitions.<sup>6</sup> Conversely, women entering the transition at older ages may have very brief transition stages or even skip stages and progress directly from regular cycles to permanent amenorrhea.

Women want to know when contraception is no longer needed and when bleeding will stop, especially when it is bothersome. In the era of personalized medicine, patients expect more from their clinicians than an imprecise 4-year window for symptoms that can both acutely affect quality of life and increase health risks. In these instances, better prediction for timing of the menopausal process is desirable. Because menopause is related to ovarian follicle depletion, a biomarker that tracks follicle supply is needed. Biomarkers that may be useful for assessing follicular depletion include follicle-stimulating hormone (FSH) and antimüllerian hormone (AMH). The Figure shows the sites of production and feedback pathways for these hormones.

FSH is produced by the pituitary, partially in response to gonadotropin-releasing hormone and partially in response to pituitary activin. FSH is also under dual inhibitory control by estradiol and the inhibin peptides A and B (inhibin B is the principal regulator of FSH in the follicular phase of the cycle; inhibin A is a product primarily of the cor-

Figure. Ovarian Follicles at Various Stages of Development



Primordial follicles are the reserve pool from which all other follicles are derived. Preantral follicles are unresponsive to follicle-stimulating hormone (FSH) and do not produce appreciable amounts of inhibin or estradiol and therefore do not exert negative feedback upon FSH. When follicles reach the antral stage, they are visible on ultrasonography. This is the beginning of follicular negative feedback upon FSH, which influences the number of follicles that grow to achieve preovulatory status. Beyond the use of ultrasonography to quantify antral follicles, serum estradiol and (less commonly) inhibin levels can be

measured. FSH can also be used as an indirect measure of the number of large follicles; here, elevated FSH results when antral follicles are diminished in number, and negative feedback is reduced. Because cycle-to-cycle variation in the number of antral follicles present in the ovary can occur, FSH levels vary cycle-to-cycle (depending on the number of antral follicles). Measurement of circulating serum antimüllerian hormone (AMH) is used to estimate the population of small growing preantral follicles. AMH levels also reflect the largest fraction of the follicle pool that can currently be measured.

pus luteum and placenta and largely contributes to FSH suppression during pregnancy). FSH is an indirect measure of follicular reserve that requires an intact hypothalamic-pituitary axis for clinically meaningful interpretation. Because FSH fluctuates almost 10-fold over the course of the normal menstrual cycle, it should be measured in a standardized fashion, typically within 5 days of the onset of menses, when it is most consistent and at its highest, to have any ability to predict the FMP. FSH levels determined within the first 5 days of the onset of menstrual bleeding are commonly used to predict ovarian response to fertility treatments. However, FSH levels are cumbersome to obtain because of the need for timed blood draws, provide only modest additional predictive value beyond menstrual-based definitions, and may be difficult to interpret because of cycle-to-cycle variation.<sup>4</sup>

AMH is a granulosa cell product secreted by the early growing ovarian follicles. It provides a more direct indicator of the ovarian oocyte ("egg") reserve. AMH peaks in women in the late-second or early-third decade of life and then declines progressively in concert with follicle loss. AMH is not produced by the population of primordial follicles in the ovary; it is only secreted once primordial follicle growth activation has occurred, but the level of AMH is proportional to the primordial reserve,<sup>7</sup> with very low levels suggestive of impending menopause.<sup>8</sup> Thus, a sufficiently sensitive AMH assay should be capable of predicting the FMP with precision.

AMH may predict how long menstruation will continue within a specified time frame. Among 121 women aged 45 to 49 years with an AMH of at least 200 ng/mL, none of them became menopausal within the next 5 years.<sup>9</sup> As with FSH, there are some caveats to the interpretation of AMH levels. Women who have longstanding hypogonadotropism or take hormones that suppress gonadotropins (such as oral contraceptives) can have falsely low AMH, and caution should be used in interpreting the test. Because AMH is a relatively new test (and the ultrasensitive test is even newer), clinical experience with its use is lacking. It is plausible that more than 1 AMH determination some months apart will provide additional information to enhance the prediction of menopause. Careful analysis of AMH levels, taking patient age and menstruation patterns into account, may eventually offer even more predictive power. These approaches will require further study and refinement.

AMH determination may plausibly influence management by helping establish that the FMP is or is not imminent. For instance, a 51-year-old woman who used a copper intrauterine device (IUD) for birth control for the past 11 years, is due for a reinsertion, and who has undetectable AMH likely has already had her FMP or, if not, it will likely occur within the next 12 months. Under these conditions, she is unlikely to require another IUD insertion. This may be particularly useful for woman using a levonorgestrel IUD or etonogestrel implant, which can result in amenorrhea. Women who are likely to have a lengthy, bothersome menopausal transition because of a young age at onset<sup>6</sup>; history of irregular menses, which makes menstrual-based definitions impossible to apply; or a high AMH level inconsistent with a diagnosis of imminent menopause (>200 ng/mL)<sup>9</sup> will be able to make a more informed decision about whether to use hormone or other prescription therapy for symptoms. On the other hand, a 48-year-old woman with endometriosis and chronic pain with an AMH level higher than 200 ng/mL is likely to have at least 5 more years of menstrual cycling; she may make an informed choice to undergo a surgical procedure (hysterectomy) rather than attempting to tolerate or temporize her symptoms with medical treatment. Women who want to know when they can stop using reversible contraception may be able to rely on an AMH level to help inform the timing.

## Conclusions

The ability to generate actionable clinical information about a woman's menopausal status and the likely timing of the FMP has improved in recent years. This is due to advances in the understanding of the endocrinology and biology (eg, ovarian follicle status) of menopause in individuals and populations. Many women will benefit from an understanding of the process and stages of their transition and their linkage to symptoms using strictly clinical criteria; however, a sizable number of women have reasons to make therapeutic decisions on the basis of the timing of their FMP. Refining approaches to biomarkers of follicular activity will likely allow more precise prediction of FMP for most women. For now, clinicians should consider patient age and menstrual criteria to predict the time course for menopause.

## ARTICLE INFORMATION

**Author Affiliations:** Department of Obstetrics and Gynecology, University of Colorado, Aurora.

**Corresponding Author:** Nanette Santoro, MD, Department of Obstetrics and Gynecology, University of Colorado, 12631 E 17th Ave, Aurora, CO 80045 (nanette.santoro@ucdenver.edu).

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