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Predicting age at menopause: Hormonal, familial, and menstrual cycle factors to consider

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eproductive aging in women natural progression through 3 stages: reproduction, the menopausal transition, and, finally, postmenopause (FIGURE).1 Most women move through the stages in this pattern, albeit at a variable rate. The menopausal transition can be divided into 2 stages: (1) early, which begins on average around age 42, and (2) late, which begins on average

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S2 From the editor CYNTHIA K. SITES, MD

S6 Diminished ovarian reserve

► KATIE ZHANG, MD, AND LUBNA PAL, MBBS, MRCOG, MS around age 46 and ends, on average, at age 51 with the final menstrual period (FMP).^{2,3} The menopausal transition is associated with diminished fertility, menstrual cycle irregularity, and vasomotor symptoms. The period that includes the menopausal transition and the first year of amenorrhea is commonly referred to as the perimenopause.

Biology of reproductive aging

Reproductive aging in women is thought to be due to the progressive decline in the quality and quantity of oocytes in primordial, intermediate, and primary follicles. Cross-sectional, histologic studies of ovaries have shown that with chronologic aging, the follicular pool (ovarian reserve) declines from its peak of 500,000 to 1,000,000 nongrowing follicles at birth to approximately 1000 at the age of menopause.4 According to a recent study, the rate of decline of nongrowing follicles progressively increases with age (eg, follicle loss occurs faster between ages 38 and 39 than between ages 30 and 31).5 A woman's age accounts for 84% of the variation in the number of nongrowing follicles, implying that ovarian age (reproductive age) is predominantly, but not exclusively, defined by chronologic age.

As the number of nongrowing follicles declines, the total number of granulosa cells declines. Fewer granulosa cells lead to decreased production of anti-Müllerian hormone (AMH) and inhibin, which are products of granulosa cells. Lower inhibin levels during the luteal and early follicular phase lead to a premature rise in follicle-stimulating hormone (FSH) and advanced follicular growth.6 The follicular phase (from onset of menses to ovulation) shortens. Thus, elevated early follicular phase FSH and estradiol levels and a shortened menstrual cycle length may be observed in women who have diminished ovarian reserve.

Hormonal changes

Because a decline in the follicular pool size leads to hormonal changes, it may be possible to measure these hormones in blood or urine and use them

CONTINUED ON PAGE S3

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FROM THE EDITOR



"When will I go through menopause?"

As the new Editor of *Menopausal Medicine*, I would first like to thank Nanette Santoro, MD, for the absolutely terrific job that she has done as Editor for the past 3 years. It is an honor and a challenge to succeed her.

One question that our patients frequently ask us, as providers of care to women in their 30s, 40s, and 50s, is: "When will I go through menopause?" The question may come from a woman who is hoping to avoid a late-life pregnancy, or has delayed childbearing and is now planning for a pregnancy, or has endometriosis or fibroids and hopes to avoid major surgery if her problems will resolve with the onset of menopause. Unfortunately, for individual women, we have no definitive answers. But it is arguably an important question to be able to answer with some certainty. A woman's mother's age at menopause and a personal history of pelvic surgery and radiation must factor into this calculation.

In this issue of *Menopausal Medicine*, Anne Z. Steiner, MD, MPH, discusses the stages of the menopausal transition and useful markers in each stage that can help women predict prospectively where they are on the continuum toward menopause. Anti-Müllerian hormone (AMH), inhibin B, early follicular phase follicle-stimulating hormone (FSH) and estradiol, and antral follicle count may all be helpful with regard to predicting the age of menopause. Perhaps combining several of these parameters might be the most accurate way to predict the final menstrual period.

Also in this issue, Katie Zhang, MD, and Lubna Pal, MBBS, MRCOG, MS, discuss how diminished ovarian reserve diagnosed in infertility patients in their 30s is not the same as declining ovarian function in women in their 40s and early 50s. Urinary hormone metabolites seem to indicate that these conditions are distinct entities.

Recent studies suggest the importance of genetics as a predictor of menopause timing. Genes associated with initial follicle recruitment, such as the anti-Müllerian hormone type II receptor, may therefore become more important as predictors of menopause age. In the future, we may be able to answer an individual patient's question about the onset of menopause more conclusively by developing a predictive model based on historical, genetic, hormonal, and environmental factors.

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CONTINUED FROM PAGE S1

FIGURE Stages of normal reproductive aging in women

Final menstrual period (FMP)

Stage	-5	-4	-3	-2	-1		+1	+2
Terminology	Reproductive			Menopausal transition		Postmenopausal		
	Early	Peak	Late	Early	Late	Early		Late
				Perimenopause				
Duration of stage	Variable			Variable		a 1 yr	b 4 years	Until demise
Menstrual cycles	Variable to regular	Reg	Regular		≥2 skipped cycles and an interval of amenorrhea (≥60 days)	Amenorrhea x 12 mo	None	
Endocrine	Normal FSH		↑FSH	↑FSH		↑FSH		

FSH = follicle-stimulating hormone.

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as indirect markers of ovarian reserve. Multiple studies have shown that AMH and early follicular phase inhibin B serum levels decline with chronologic age.7-9 Early follicular phase FSH levels appear to increase with chronologic age. In a longitudinal study, Ferrell et al showed that between the ages of 26 and 58, an individual woman's FSH levels will rise from baseline levels over 5-year intervals.10 de Vet et al demonstrated a decline in AMH over a 2-year interval in women aged 20 to 35 years at baseline; no changes in FSH were observed during this interval in these younger women.11

Antral follicle count

Serum AMH levels directly correlate with the antral follicle count (AFC) as measured by transvaginal ultrasound. ¹² The number of antral follicles is thought to be proportional to the number of nongrowing follicles in the ovary. As further proof, Hansen et al showed that the AFC and serum early follicular phase AMH, inhibin B, and

FSH levels correlate with primordial follicle counts (histologically determined following oophorectomy). The AFC and AMH correlated with the ovarian primordial follicle count independent of age.

Ovarian reserve and fertility

Since ovarian reserve is thought to determine the reproductive stage, markers of ovarian reserve have been proposed as potential predictors of a woman's reproductive stage. Although no studies have determined the ability of markers of ovarian aging to predict age-related infertility in the general population, these markers are used clinically in women with infertility to predict response to and potential success of fertility treatments such as in vitro fertilization. Early follicular phase serum FSH (menstrual cycle day 2, 3, or 4) has classically been measured for this purpose. An emerging body of literature also supports the measurement of AMH for this purpose. While measurement of FSH must be timed by the menstrual cycle, AMH can be sampled at any phase of the menstrual cycle.¹³

Variables associated with age at menopause

Markers that predict age at menopause or time to the FMP would be of significant value to women and clinicians. Time to menopause could influence treatment choice (medical or surgical) for women with disorders of menstruation. While no single test can predict age at menopause, factors that have been associated with age at menopause include chronologic age, mother's age at menopause, menstrual cycle characteristics, and markers of ovarian reserve.

Chronologic age: Like mother, like daughter

The median age at menopause is 51. 14,15 Approximately 1% of women will reach menopause by age 40, 10% by age 46, and 90% by age 55. 15 In addition to population estimates, a woman's mother's age at menopause may

provide some guidance as to when the woman will experience her final menstrual period. Multiple studies have shown an association between a mother's and a daughter's age at menopause. ^{16,17} The earlier the mother experiences menopause, the poorer the ovarian reserve in the daughter between ages 35 and 49. ¹⁸

This commonality may be due to genetics or shared behaviors, such as tobacco use, dietary intake, and physical activities. A genetic hypothesis is supported by twin studies, which attribute 63% of the concordance to shared genetic material.19 Pedigree analyses have revealed a potential dominant pattern of inheritance of early menopause (defined as menopause between ages 40 and 45) and premature ovarian failure (defined as menopause prior to age 40) through maternal or paternal relatives.20,21 A potential familial cause of early menopause and premature ovarian failure is alteration in the FMR1 gene. The length of the trinucleotide repeat, CGG, in the FMR1 gene has been correlated with age at menopause.²² Women with longer repeat sequences have earlier onset of menopause, and women with shorter sequences have later onset.

Menstrual cycle characteristics

Certain menstrual cycle characteristics are also associated with time to the FMP. The early menopausal transition is defined by a change in menstrual cycle length by 7 or more days. The late menopausal transition is defined by 2 or more skipped cycles or an interval of amenorrhea of 60 or more days. The median time from the onset of increased menstrual cycle length variability to the FMP is approximately 7 years, ²³ and the median time from the late menopausal transition (missed cycles) to the FMP is approximately 4 years. ¹⁵ However, about

10% of women will enter menopause with no history of prolonged menstrual cycle irregularity. 15,23

Markers of ovarian reserve

Prediction of age at menopause can be further enhanced using markers of ovarian reserve. Studies of follicular phase hormone levels have shown an association with reproductive stage (reproductive, early menopausal transition, late menopausal transition, and postmenopause) as defined by menstrual cycle characteristics. Early follicular phase hormone levels that have been associated with reproductive stage include estradiol, FSH, inhibin B, and AMH; however, a single hormone does not appear to differentiate each stage. AMH appears to differentiate the early stages: premenopausal to late transition. However, AMH levels appear to drop below detection during the late transition; therefore, AMH levels may be less useful in determining late transition from menopause onset.24,25 Conversely, early follicular phase estradiol levels differ in late stages. Only with the onset of menopause do estradiol levels drop significantly; a rise in early follicular phase estradiol levels may be observed during the late menopausal transition.^{26,27}

A consistent pattern of change in FSH and inhibin B levels across the stages of reproductive aging has not been observed. Most studies show that FSH rises from the early menopausal transition to postmenopause, 26,28,29 but subtle changes may be observed earlier (between the late reproductive stage and the early menopausal transition).26,29 The rate of change in FSH may also predict time to the FMP. Sowers et al showed that FSH rose modestly before 7 years prior to the FMP, with a major acceleration in rise between 7 and 2 years prior to the FMP, and an acute increase in rise between 2 years prior and 1 year following the FMP.³⁰ Some studies have found that inhibin B levels start to decline early in the menopausal transition, ^{25,28,31} but others have shown that they declined only late in the transition.^{24,32}

Determining a woman's reproductive stage

While one cannot use a single test to determine time to the FMP, the menstrual cycle pattern and hormonal characteristics can be used to generate rough estimates for counseling patients.

The reproductive, premenopausal stage is generally characterized by regular menstrual cycles, early follicular phase FSH levels less than 10 mIU/mL, and AMH levels greater than 0.3 ng/mL.

The early menopausal transition begins approximately 7 to 8 years prior to the FMP. It is characterized by increased variability in the menstrual cycle length. Classically, it involves shortening of the menstrual cycle. FSH values are generally greater than 10 mIU/mL, and AMH levels are less than 0.4 ng/mL in this group of women. ^{26,29}

The late menopausal transition begins approximately 3 to 4 years prior to the FMP. This stage begins when 2 or more menstrual cycles are skipped or a woman experiences 60 or more days of amenorrhea. Occurrence of the late menopausal transition stage is further confirmed when early follicular phase estradiol levels are greater than 100 pg/mL or FSH values are greater than 30 to 40 mIU/mL.^{26,33} Other studies use lower FSH level cutoffs (15 mIU/mL) for the late transition.29 Differences in cutoff levels may be due to FSH assay characteristics. AMH values are generally less than 0.1 ng/mL (or below assay sensitivity).25

Menopause. While the term *menopause* appears easy to define as "12



months of amenorrhea," differentiating women in the late menopausal transition from those in early postmenopause can be difficult within the first 12 months following the FMP. Menstrual cycle characteristics may be helpful. Approximately 91% of women with 6 months of amenorrhea will subsequently be determined to be postmenopausal.34 Additional hormonal testing may be of limited benefit. FSH levels do not rise acutely following the FMP. Although the rise in luteinizing hormone (LH) tends to follow that of FSH, some studies have not found a significant difference in LH levels between women in the late transition and those in early postmenopause.²⁹

Limitations and uses of predictors

Predictors do have their limitations. Approximately 10% of women will have regular menstrual periods up to the time of their FMP.15 Most predictors have not been studied in women younger than 30 years of age; therefore, use of predictors in this age group should be avoided. While repetitive testing is, in general, of little value, women in their 40s can exhibit significant intercycle variability. In this group, a normal FSH value should be viewed with caution and confirmed with repeat testing. The highest measured FSH value is thought to reflect a woman's current ovarian reserve, even if subsequent values are lower.

In summary, while a number of predictors of age at menopause have been identified, no single test or formula can be used to calculate the FMP. Reliance on one parameter to define time to the FMP should be avoided. Predictors should be used in combination and in context for general counseling purposes. Expensive laboratory testing is unnecessary unless results will influence health or treatment choice.

Finally, although pregnancy is less common in the early perimenopause transition, conception can occur. Women should be advised to continue to use birth control during this time if they desire to avoid pregnancy. Conversely, a single test result generally should not be used as a method for defining or denying treatment, such as for infertility.

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Diminished ovarian reserve: Accelerated reproductive senescence or a distinct paradigm in reproductive aging?

► KATIE ZHANG, MD, AND LUBNA PAL, MBBS, MRCOG, MS

he reproductive span has long been viewed somewhat simplistically as relatively uniform periods of prepubertal, reproductive, and postreproductive life. Relatively recently, the premenopausal period has been recognized as heterogeneous.¹ New-onset menstrual cycle disturbances/irregularity and vasomotor symptoms herald the menopausal transition, whereas cessation of menses marks the onset of a new beginning, that is, menopause.

Defining ovarian reserve and its decline

The evolution of the field of assisted reproduction and the expanded approaches available for evaluating the infertile couple have contributed to an appreciation of the "ovarian reserve," a concept that refers to the quantity and quality of available oocytes. A decline in ovarian reserve accompanies chron-

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ologic aging and can be detected with the use of several available biomarkers.²

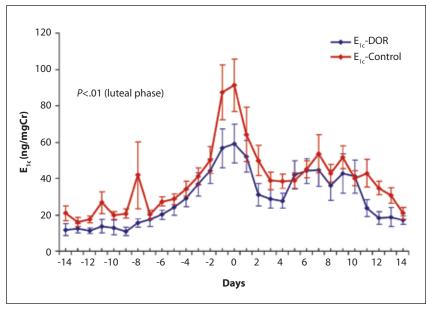
Although controversy exists regarding an absolute definition of diminished ovarian reserve (DOR), this state is characterized by suboptimal quantitative ovarian response to ovarian hyperstimulation protocols and poor prognosis for reproductive success.³

Premature ovarian failure, or premature ovarian insufficiency (POI)—a more recent and preferred term, and

surgical menopause are recognized as extreme examples of a truncated reproductive life span, with short- and long-term implications. A Recently, limited data suggest that young women with DOR are destined for accelerated reproductive senescence.

A number of factors have been associated with diminished ovarian reserve, including genetics (fragile X premutation carriers are known to manifest biochemical evidence of

FIGURE 1 Urinary levels of estrone conjugate



Diminished ovarian reserve (DOR) is suggested as a state of "relative hypoestrogenism" as reflected by urinary levels of estrone conjugate (E_{12}), as assessed by daily profile of urinary levels across an entire menstrual cycle. The differences between the 2 groups (women with DOR and controls) are of statistical significance for the luteal phase of the menstrual cycle (P<.01). Note: Centering of cycles relative to the luteinizing hormone (LH) surge (day 0).

Data are presented as mean (SEM).

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DOR and are at risk for POI), exogenous factors (eg, smoking), and iatrogenic risks (chemo-radiation and pelvic surgery). Although chronic stress has been suggested to be associated with an increased likelihood for a DOR diagnosis, the cause-effect relationship of this observation remains unclear.

Characteristics of DOR

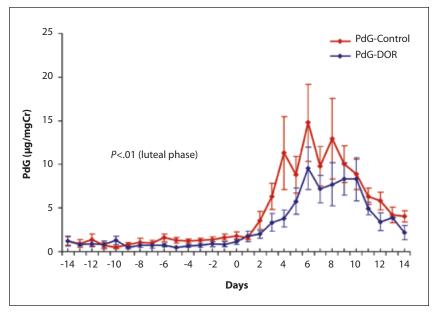
The phenotype of DOR is well recognized in regularly menstruating women undergoing infertility treatment. Women with compromised ovarian reserve have elevated early follicular phase serum follicle-stimulating hormone (FSH) levels, concomitantly reduced serum levels of anti-Müllerian hormone and inhibin B, and reduced numbers of ovarian antral follicles.²

Blunted quantitative ovarian response to ovarian stimulation attempts, despite the use of increasing doses of exogenous gonadotropins, is the diagnostic hallmark of DOR. The reproductive physiology of DOR offers additional characteristic signatures, such as a shortened follicular phase and a suboptimal ovarian endocrine milieu (lower serum estradiol levels and fewer developing follicles) following administration of exogenous gonadotropins.

Hormonal nuances in women with DOR vs controls

Of interest is our recent study on the reproductive hormonal milieu in infertile women with DOR.⁷ We assessed the spectrum of urinary levels of reproductive hormones (FSH, luteinizing hormone [LH], and metabolites of estrogen and progesterone) in daily urine specimens collected across a spontaneous menstrual cycle in 8 young infertile women diagnosed with DOR and in 14 healthy age-comparable controls.⁷

FIGURE 2 Urinary levels of progesterone metabolite PdG



Evidence of luteal insufficiency in premenopausal women with diminished ovarian reserve (DOR) is suggested by daily profile of urinary levels of progesterone metabolite PdG across an entire menstrual cycle compared with controls (*P*<.01). Note: Centering of cycles relative to the luteinizing hormone (LH) surge (day 0).

Data are presented as mean (SEM).

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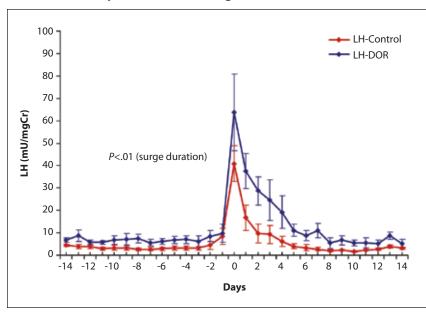
Statistically significant attenuations in the urinary estrone conjugate (E_{1c}), an estrogen metabolite, and in urinary pregnanediol-di-glucoronide (PdG), a progesterone metabolite, were observed in women with DOR compared with controls (FIGURES 1 AND 2). In addition, protracted surges of LH were evident in the DOR group compared with the controls (FIGURE 3). These data identify DOR as a state of relative hypoestrogenism and luteal insufficiency.

DOR as a distinct state

Having thus identified perturbations in the hypothalamic-pituitary and ovarian axes in the setting of DOR, we have more recently attempted to explore whether DOR represents accelerated reproductive aging. If this is indeed true, then the endocrine milieu of women with DOR would resemble that observed in chronologically older women traversing the reproductive aging spectrum.

We used the urinary reproductive hormone profiles of the young premenopausal infertile women (age range, 32 to 37 years) with DOR described in the above study and compared them with the urinary hormone profiles of 11 chronologically older (age range, 43 to 52 years) perimenopausal historic controls. The 2 groups had distinct reproductive hormone profiles: the urinary estrogen metabolites in the premenopausal women with DOR were significantly lower than those observed in the older cohort.8 On one hand, these data identify DOR as a hypoestrogenic state; on the other, they imply that DOR is a distinct state within the currently understood continuum of reproductive aging.9

FIGURE 3 Urinary levels of luteinizing hormone



A robust and protracted urinary luteinizing hormone (LH) surge was observed in women with diminished ovarian reserve (DOR) compared with controls, as assessed by daily profile of urinary levels across an entire menstrual cycle. The differences between the 2 groups are of statistical significance for the duration of the LH surge (P<.01). Note: Centering of cycles relative to the LH surge (day 0).

Data are presented as mean (SEM).

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Long-term health implications of DOR

Beyond the reproductive challenges faced by women who have compromised ovarian reserve, the observed hypoestrogenism in the setting of DOR may contribute to the development of chronic morbidities, such as osteoporosis and coronary vascular disease (CVD), that are associated

with estrogen deprivation and are prevalent in postmenopausal women. Indeed, compromised ovarian reserve has been identified as a risk factor for low bone mass¹⁰ and has been shown to relate to surrogate markers for risk of CVD.^{11,12}

In summary, limited data identify DOR as being distinct from chronologic aging. The relative hypoestrogenism

in otherwise healthy-appearing young women may pose future health challenges that merit quantification and preemptive management to minimize the burden of future morbidities.

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