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What is menopause?

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In this first article, we set the stage for understanding the physiology of menopause, an important and virtually inevitable physiologic experience for all living, reproductively competent women.[1] Usually a midlife event, menopause coincides with and can be complicated by myriad health, family, work, relationship, and economic issues. It is vital that all healthcare professionals are familiar with this universal, natural transition and confident in reassuring their patients born with ovaries that a wide variety of individual experiences is normal and that many approaches are available to address bothersome symptoms and signs.

WHAT IS MENOPAUSE?

When considered from the totality of a woman's lifespan, menopause is a single point in time, formally defined as the final menstrual period, diagnosed retrospectively after 12 months of amenorrhea (absence of menstrual cycles).[2]

WHAT CAUSES MENOPAUSE?

The basis of reproductive senescence in women is oocyte depletion of the ovary.[2,3] In utero, the number of ovarian follicles peaks at approximately 7 months gestation, and before birth, through atresia, the follicle number declines to approximately 1 million follicles.[4] Follicular atresia occurs continuously even during pregnancy and oral contraceptive use. Atresia accelerates with increasing age, until by age 52, the average age of menopause, approximately 1,000 follicles remain. Estradiol secretion is no longer adequate to stimulate the uterine lining, and menopause occurs.

WHAT FACTORS CAN ACCELERATE OOCYTE DEPLETION?

As a lifestyle factor, smoking can hasten menopause. Factors that contribute to premature (<40 y) menopause include iatrogenic causes (bilateral oophorectomy; cancer treatments [chemotherapy and radiation therapy; pelvic surgeries]); inborn errors of metabolism (galactosemia); genetic abnormalities (Turner syndrome and fragile X premutation); autoimmune disorders, including polyendocrine disorders; toxic exposures (endocrine-disrupting chemicals); and infectious etiologies (mumps, HIV).[5]

WHY IS MENOPAUSE IMPORTANT?

By 2030, 1.2 billion women globally will have reached menopause. In the United States, 6,000 women transition to menopause daily. Up to 80% of women report vasomotor symptoms (VMS) or hot flashes. Some experience symptoms for a decade or more before menopause, with persistent symptoms for some lasting more than a decade afterward. Additional symptoms include irregular uterine bleeding, disrupted sleep, mood disorders, difficulty concentrating, and impaired short-term memory. Symptoms can be associated with higher healthcare costs and loss of work productivity. Evidenced-based therapies for symptom relief are available. The Study of Women's Health Across the Nation, a longitudinal study of women traversing menopause, has shown that Black women have the longest duration of VMS (10 y; followed by White women [9 y]; and Chinese or Hispanic women [5 y]).[6] Emerging data suggest that the menopause experience of indigenous women appears to be the most symptomatic of groups that have been studied.

WHEN DOES MENOPAUSE OCCUR?

For most women, menopause occurs in midlife, between the ages of 45 and 56 years. Early menopause, occurring from ages 40 to less than 45 years, is associated with increased cardiovascular disease, congestive heart failure, and diabetes. Whether these conditions reflect early loss of endogenous estrogen or genetic contributions to premature aging, of which menopause is just one manifestation, is a topic of ongoing study. Without treatment, early and premature menopause are associated with increased risks of cardiovascular disease, cognitive decline, and osteoporosis.[5]

WHAT HAPPENS DURING THE TRANSITION FROM MENSTRUAL CYCLES TO MENOPAUSE?

Perimenopause is the term that describes the years before menopause when menstrual cycles start to change (>7 d difference in cycle length early in the transition, and later, episodes of amenorrhea lasting >2 mo); it includes the first year after the final menstrual period.[2] During this transition, women can experience additional symptoms such as VMS (hot flashes); mood changes, including depressive symptoms; sleep disruption; vaginal dryness; possible discomfort with intercourse; and recurrent urinary tract infections. Bone loss begins before the final menstrual period.[6]

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WHAT ARE THE STAGES OF REPRODUCTIVE AGING?

The Stages of Reproductive Aging provide a framework with standardized, objective criteria to define stages (reproductive, menopause transition, and postmenopause) for clinical and research purposes.[2] The duration of each phase varies individually, as do associated symptoms. The phases are defined based on menstrual cycles and symptoms without hormone determinations. Endocrine hormone measurements are usually unnecessary for diagnosing menopause. Vasomotor symptoms usually present in the late menopause transition concurrently with episodes of more than 2 months of amenorrhea and in the early postmenopause phase. Vaginal dryness more commonly presents later.

HOW DO YOU KNOW IF A WOMAN IS PERIMENOPAUSAL?

No one symptom or test is accurate enough by itself to rule in or rule out perimenopause. Clinicians should diagnose perimenopause based on menstrual history, age, and symptoms such as hot flashes without relying on laboratory test results.[7]

WHAT HORMONE CHANGES CHARACTERIZE THE MENOPAUSE TRANSITION?

The progressive decline of ovarian follicle numbers results in reduced inhibin secreted by the granulosa cells. Inhibin inhibits the synthesis and release of follicle-stimulating hormone (FSH) from the pituitary gland. Thus, with the decline of the number of ovarian follicles, inhibin decreases and FSH becomes elevated. The decline in estradiol production because of diminishing ovarian follicles also reduces pituitary negative feedback, and FSH increases further. Hormone shifts during the menopause transition can be erratic (including transient elevated estradiol levels). Ovarian progesterone secretion often declines before menopause, even during ovulatory cycles. Testosterone declines with age as do adrenal androgens. After menopause, the dominant serum estrogen shifts from estradiol to estrone; both FSH and luteinizing hormone are elevated.

WHAT ARE THE CONSEQUENCES OF MENOPAUSE?

Menopause liberates women from the inconvenience and discomfort of monthly menstrual cycles, associated mood swings, and concerns with contraception and risk of unintended pregnancy. On the downside, the decline in ovarian estradiol production is associated with symptoms that range from mild to debilitating[7] and metabolic changes that can increase bone loss and cardiovascular risk.[6,8]

KEY SUMMARY POINTS

1. Ovarian aging results in profound reduction of ovarian follicles and estradiol production, loss of fertility, and absence of menstrual cycles.
2. Symptoms that vary in severity from person to person commonly arise during the years before and after menopause.
3. Quality of life, including work effectiveness, can be negatively affected by the transition to menopause.
4. Clinician familiarity with signs and symptoms of the menopause transition aid in recognition, reassurance, and counseling regarding options for symptom relief and preventive strategies for long-term health.

CLINICAL RECOMMENDATIONS

1. Recognize that menopause is a universal transition for midlife women with symptoms and potential long-term health consequences.
2. Initiate a discussion anticipating the menopause transition with all women aged 35 to 40 years or older.
3. Encourage patients to monitor and report menstrual cycle regularity at every visit; investigate episodes of amenorrhea (> 3-6 m) in women aged younger than 45 years (pregnancy test, thyroid stimulating hormone, prolactin, and follicle-stimulating hormone) before making diagnosis of premature or early menopause.[5]
4. Establish an ongoing dialogue regarding expectations, symptoms and signs experienced, and personal preferences for management, if necessary.

Coming next in the *Menopause Step-by-Step* series: Nanette Santoro, MD, Professor and E. Stewart Taylor Chair, Divisions of Reproductive Endocrinology and Infertility and Reproductive Sciences, Department of Obstetrics and Gynecology, University of Colorado, discusses clinical aspects of perimenopause, including evidence-based symptom management, contraceptive options, and transitioning to menopause.

This article is part of the ongoing series *Menopause Step-by-Step*, a monthly *Menopause* education feature. The accompanying editorial explaining this series can be found here: doi: 10.1097/GME.0000000000002417

REFERENCES

1. Stuenkel CA, Kinney CC, Schiff I. *Menopause Step-by-Step:* A new monthly *Menopause* education feature. *Menopause* 2024;31:737-740. doi: 10.1097/GME.0000000000002417
2. Harlow SD, Gass M, Hall JE, et al. STRAW +10 Collaborative Group. Executive summary of the Stages of Reproductive Aging Workshop +10: addressing the unfinished agenda of staging reproductive aging. *Menopause* 2012;19:387-395. doi: 10.1097/gme.0b013e31824d8f40
3. Cappola AR, Auchus RJ, El-Hajj Fuleihan G, et al. Hormones and aging: an Endocrine Society scientific statement. *J Clin Endocrinol Metab* 2023;108:1835-1874. doi: 10.1210/clinem/dgad225
4. Hansen KR, Knowlton NS, Thyer AC, Charleston JS, Soules MR, Klein NA. A new model of reproductive aging: the decline in ovarian non-growing follicle number from birth to menopause. *Hum Reprod* 2008;23:699-708. doi: 10.1093/humrep/dem408
5. Stuenkel CA, Gompel A. Primary ovarian insufficiency. *N Engl J Med* 2023;388:154-163. doi: 10.1056/NEJMcp2116488
6. El Khoudary SR, Greendale G, Crawford SL, et al. The menopause transition and women's health at midlife: a progress report from the Study of Women's Health Across the Nation (SWAN). *Menopause* 2019;26:1213-1227. doi: 10.1097/GME.0000000000001424
7. Santoro N, Roeca C, Peters BA, Neal-Perry G. The menopause transition: signs, symptoms, and management options. *J Clin Endocrinol Metab* 2021;106:1-15. doi: 10.1210/clinem/dgaa764
8. El Khoudary SR, Aggarwal B, Beckie TM, et al, American Heart Association Prevention Science Committee of the Council on Epidemiology and Prevention; and Council on Cardiovascular and Stroke Nursing. Menopause transition and cardiovascular disease risk: implications for timing of early prevention: a scientific statement from the American Heart Association. *Circulation* 2020;142:e506-e532. doi: 10.1161/CIR.0000000000000912