

As each woman moves from the reproductive phase of life through the menopause transition into the postmenopausal years, a number of physical and psychological changes may occur. Clinicians may be challenged to differentiate changes related to menopause from those related to aging. Several hormonal systems manifest age-related changes that may or may not have their onset during the menopause transition. Furthermore, medical conditions such as obesity, diabetes, lipid disorders, thyroid disorders, and hypertension often develop or worsen during midlife.

Age at menopause

In the Western world, spontaneous menopause occurs at an average age of 51.4 years, with a Gaussian distribution ranging roughly from 40 to 60 years. Extremes in age at menopause are rare and are often associated with other medical conditions. Menopause in a woman younger than 40 years of age constitutes premature ovarian failure. No set age formally constitutes “delayed menopause,” but a woman well past the usual age of menopause with irregular vaginal bleeding should be evaluated to rule out gynecologic

and possible endocrine or hematologic disorders. (See Section D for more about premature menopause.)

Although women today enjoy an increase in life expectancy, the average age of natural menopause has not substantially changed during the past few centuries, even with improved nutrition and reduction of disease. Age at menopause is influenced by multiple genetic and environmental factors.

Earlier menopause can be induced by factors that accelerate ovarian follicular atresia (cell death and degeneration). Genetic variations, ovarian “toxins” such as smoking, metabolic disorders, autoimmune syndromes, HIV infection, and cancer therapies, as well as lifestyle variables, may contribute. The dose and duration of exposure are important. Aberrations in central neuroendocrine control of reproduction might also alter the timing of menopause. See Tables 1 and 2.

To predict the age of menopause, a model has been proposed that incorporates the number of full-term pregnancies, body mass index, history of breast surgery, and the presence of either of two specific single nucleotide polymorphisms of estrogen-metabolizing genes (CYP17 or CYP1B1-4).

Table 1. Genetic and environmental factors affecting age at menopause

Genetic variations

- Alterations in the X-chromosome and possibly in chromosome 9.
- Polymorphisms (common genetic variations in DNA) of estrogen receptor- α .
- Polymorphisms of estrogen-metabolizing genes.

Environmental exposure

- Current smoking accelerates age of menopause by approximately 1.5 years with a dose-response relationship between the number of cigarettes smoked, the duration of smoking, and age at menopause.
- Survivors of childhood cancers have an 8% incidence of premature menopause compared with 0.8% in siblings. Risk factors include ovarian exposure to increasing doses of radiation, number of alkylating agents and cumulative dose, and the diagnosis of Hodgkin's lymphoma.

Lifestyle and concurrent medical conditions

- Nulliparity may be associated with earlier menopause.
- In the Framingham Heart Study cohort, each 1% higher premenopausal Framingham risk score for cardiovascular risk was associated with a 1.8-year decrease in the age at menopause, suggesting that heart disease risk factors influence the age of menopause, rather than the converse. In the prospective evaluation of women during the menopause transition—the

Study of Women's Health Across the Nation (SWAN)—a history of heart disease was independently associated with earlier menopause.

- In one report, women with type 1 diabetes mellitus (DM) experienced menopause approximately 8 years earlier than their female siblings without DM; those with type 2 DM did not experience an earlier menopause.
- Women with epilepsy have an increased risk for developing menopause earlier. Women who experienced menopause earlier were more likely to have had exacerbation of their seizures.
- In a study of Latin American women, women living at high altitudes had earlier menopause.
- In an Italian cohort, season of birth was associated with timing of menopause. The earliest age of menopause was in women born in March; the latest was among those born in October.
- Adverse socioeconomic conditions across the life span, measured in terms of economic hardship and low educational attainment, may be associated with an earlier perimenopause.
- Being separated, widowed, divorced, or unemployed was associated with earlier natural menopause in SWAN.
- Women with a lifetime history of major depression, particularly if accompanied by the use of antidepressants, had nearly three times the risk of an earlier perimenopause.