

Menopause is a natural biologic process, not an estrogen deficiency disease. Menopause represents the permanent cessation of menses resulting from loss of ovarian follicular function. Menopause can occur spontaneously (or naturally) or be induced through a medical intervention (surgery, chemotherapy, or pelvic radiation therapy).

Aging is the natural progression of changes in structure and function that occur with the passage of time in the absence of known disease. Aging of the female reproductive system begins at birth and proceeds as a continuum. It consists of a steady loss of oocytes from atresia or ovulation, which does not necessarily occur at a constant rate. Because of the relatively wide age range (40-58 years old) for spontaneous menopause, chronologic age is a poor indicator of the beginning or the end of the menopause transition.

Menopause and its physical and psychological consequences are a significant public health issue because of three factors: (1) menopause affects every woman, (2) an unprecedented number of women are postmenopausal, and (3) more postmenopausal women are living beyond age 65.

A woman's life expectancy in the Western world is estimated at 79.7 years. Today, a woman who reaches age 54 can expect to reach age 84.3. About two-thirds of the total U.S. population is expected to survive to age 85 or longer.

Terminology

Clinicians and researchers in the field of menopause have long recognized the need for universally accepted

menopause terminology as well as a staging system to divide the last 10 to 15 years of reproductive aging. In 2001, the Stages of Reproductive Aging Workshop (STRAW) sponsored by The North American Menopause Society (NAMS), the National Institutes of Health, the American Society for Reproductive Medicine, and the National Institute of Child Health and Human Development, addressed nomenclature and a staging system. Previously, the Council of Affiliated Menopause Societies (CAMS), an international policy organ of the International Menopause Society, had developed standardized definitions for menopause-related events. Although STRAW redefined some terms, other CAMS terms remain in use.

The reproductive aging continuum created by STRAW is divided into seven stages; five precede and two follow the final menstrual period (FMP) (see Fig 1). STRAW points out, however, that not all healthy women will follow this pattern; some will seesaw between stages or skip a stage altogether.

Menopause. The term *menopause* (ie, *spontaneous* or *natural menopause*), as defined by STRAW, is recognized to have occurred after 12 months of amenorrhea and for which there is no obvious pathological cause. It reflects a near-complete but natural diminution of ovarian hormone secretion. There is no adequate independent biological marker for menopause.

Menopause is one point in time. The phrases “in menopause” and “going through menopause” are misnomers sometimes used to describe perimenopause or the menopause transition. It is appropriate to say that one “reaches” menopause.

Figure 1. Stages/nomenclature of normal reproductive aging in women

	Final Menstrual Period (FMP)							
Stages:	-5	-4	-3	-2	-1	0	+1	+2
Terminology:	Reproductive			Menopausal Transition		Postmenopause		
	Early	Peak	Late	Early	Late*	Early*	Late*	
				Perimenopause				
Duration of Stage:	variable			variable		Ⓐ 1 yr	Ⓑ 4 yrs	until demise
Menstrual Cycles:	variable to regular	regular		variable cycle length (>7 days different from normal)	≥2 skipped cycles and an interval of amenorrhea (≥60 days)	Amen. x 12 mos	none	
Endocrine:	normal FSH		↑ FSH	↑ FSH		↑ FSH		

*Stages most likely to be characterized by vasomotor symptoms.

Source: Stages of Reproductive Aging Workshop (STRAW), *Menopause* 2001.

Premenopause. The term *premenopause* is often used ambiguously. CAMS recommends that this term encompass the entire reproductive period up to the FMP. NAMS uses the term to refer to the time prior to beginning of perimenopause. Because the term can be confusing, CAMS recommends that it be abandoned. STRAW did not use this term.

Perimenopause. The term *perimenopause*, according to STRAW, is defined as about or around menopause. It begins with Stage -2 and ends 12 months after the FMP. Although STRAW suggests that the term *perimenopause* be used only with patients or in the lay press, NAMS prefers to use the term with all audiences. NAMS also uses the term interchangeably with *menopause transition*.

Menopause transition. According to STRAW, the term *menopause transition* (or *menopausal transition*) is defined as the span of time from Stage -2 (early) through Stage -1 (late). During this time, menstrual cycle and endocrine changes are observed. The *menopause transition* begins with variation in menstrual cycle length from a rise in levels of monotropic follicle-stimulating hormone (FSH) and ends with the FMP (which is recognized only after 12 consecutive months of amenorrhea). Women experiencing induced menopause do not go through a menopause transition.

Postmenopause. The term *postmenopause* is the span of time dating from the FMP, regardless of whether menopause was spontaneous or induced. It is defined by STRAW as extending from Stage +1 (early) through Stage +2 (late).

Stage +1 is defined as within 5 years after the FMP. During Stage +1, further dampening of ovarian hormone function occurs, resulting in a permanently low level. Stage +1 is also the time of accelerated bone loss. STRAW further divided Stage +1 into segments “a” (the first 12 months after the FMP) and “b” (the next 4 years). Stage +2 has a definite beginning (5 years after the FMP), but its duration is variable inasmuch as it ends with the woman’s death. STRAW concluded that further divisions may be warranted as more information is accumulated about the physiology of menopause.

Climacteric. STRAW suggests that the term *climacteric* be used interchangeably with *perimenopause*. However, CAMS defines climacteric as the age-related transition in women from the reproductive to the nonreproductive state. It is a process rather than a specific point in time. According to CAMS, the climacteric for women is sometimes, but not necessarily always, associated with symptomatology. When this occurs, it may be termed the *climacteric syndrome*.

STRAW has suggested that the term *climacteric* not be used in scientific papers. Global consensus on this terminology has not been achieved. NAMS does not use the term, but it is still widely used outside North America.

Premature menopause. According to CAMS, *premature menopause* should be defined as spontaneous menopause that occurs at an age less than 2 standard deviations below the mean estimated age for the reference population. In practice, CAMS states, the age of 40 is frequently used as an arbitrary cutoff point below which menopause is said to be premature.

NAMS uses the term *premature menopause* to describe menopause reached at or under age 40, whether menopause is spontaneous or induced.

Premature ovarian failure. The term *premature ovarian failure* (POF) is used to describe ovarian insufficiency leading to amenorrhea that occurs in women younger than age 40. POF can be transient (from causes such as over-exercising, eating disorders, or high levels of stress) or permanent (from causes such as autoimmune disease or genetic abnormalities). When permanent, POF is equivalent to premature menopause.

Induced menopause. According to CAMS, the term *induced menopause* is defined as the cessation of menstruation that follows either surgical removal of both ovaries (bilateral oophorectomy, with or without hysterectomy) or iatrogenic ablation of ovarian function (eg, by chemotherapy or pelvic radiation therapy). Bilateral oophorectomy is the most common cause of induced menopause.

In women who experience surgically induced menopause (*surgical menopause*), fertility ends abruptly. With other types of induced menopause, fertility may end immediately or over several months.

Temporary menopause. The term *temporary menopause* is used to describe a span of time when normal ovarian function is interrupted and temporary amenorrhea results. Since menopause is by definition the very last menses, NAMS recommends that the term *temporary menopause* be abandoned.

Age at menopause

In the Western world, spontaneous menopause occurs at an average age of 51.4 years, with a Gaussian distribution ranging from 40 to 58 years. Some women reach menopause in their 30s and a few in their 60s. The median age for the onset of the menopause transition is 47.5 years. For most women, the transition lasts approximately 4 years. About 10% of women cease menstruating abruptly without experiencing menstrual irregularity.

Although there has been an increase in life expectancy over the years, the average age of spontaneous menopause has not changed during the past few centuries, even with improving nutrition and reduction of disease.

Two factors that influence the timing of menopause have been identified:

- Current smoking has been identified as a cause of earlier menopause, producing a shift of approximately 1.5 years. There is a dose-response relationship between the number of cigarettes smoked, the duration of smoking, and age at menopause.
- Familial factors as well as genetic polymorphisms of the estrogen receptor influence the age of onset of the menopause transition.

Limited data support the association of menopause timing with the following:

Menopause later than average age

- Multiparity (ie, more than one pregnancy),
- Increased body mass index,
- High cognitive scores in childhood;

Menopause earlier than average age

- Nulliparity (ie, history of no pregnancy),
- Medically treated depression,
- Toxic chemical exposure,
- Treatment of childhood cancer with pelvic radiation and alkylating agents,
- Epilepsy, especially in women with high lifetime seizure frequency.

No link has been found between age at menopause and use of oral contraceptives, socioeconomic or marital status, race, or age at menarche.

Epidemiology

Specific data on the overall number of postmenopausal women and those reaching menopause each year are not known. To provide estimates, NAMS has extrapolated data from several sources to determine the number of postmenopausal women by age and by surgically induced menopause and premature menopause.

<i>Total number (prevalence)</i>	<i>(in millions)</i>
Aged 51 and older ¹	39.944
Aged 40 to 50 (spontaneous menopause)	3.123
Surgical menopause ²	2.000
Premature spontaneous menopause ³	0.504
Total	45.571
<i>Total reaching menopause during 2000</i>	
Aged 51 and older	1.796
Surgical menopause ²	0.263
Premature spontaneous menopause	?
Total	2.059
<i>Total/day reaching menopause during 2000</i>	5,700

¹ Includes women who may have experienced menopause earlier in life (induced or premature spontaneous menopause).
² Includes only women younger than 50.
³ Includes only women younger than 40.
 Source: U.S. Census Bureau, 2000 Census.

United States. In 2000, there were an estimated 45.6 million postmenopausal women in the United States. About 39.9 million of them were older than age 51, the average age of spontaneous menopause in the Western world. By the year 2020, the number of U.S. women older than age 51 is expected to be more than 50 million.

NAMS has calculated estimates for the number of postmenopausal women (see Table 1), extrapolating data from the 2000 U.S. Census and other resources. Details regarding the calculation of these estimates follow.

Postmenopause by age. Nearly 40 million U.S. women are past the average age of spontaneous menopause, which is approximately 51 years in the Western world. Although the U.S. Census Bureau year 2000 report does not provide the exact number of women over 51, it does report numbers for women aged 55 and older, who can all be assumed to be postmenopausal. In addition, an estimated 75% of women in the 50- to 55-age bracket would be postmenopausal. It should be noted that these numbers include women who may have experienced induced or premature spontaneous menopause earlier in life.

Among women aged 40 to 45, an estimated 5% would have experienced spontaneous menopause, based primarily on data from the Study of Women Across the Nation (SWAN). For spontaneous postmenopausal women aged 45 to 55, a rough estimate of 25% of that population was used.

For a 1-year estimate of the number of women experiencing spontaneous menopause during 2000, the number of women aged 50 to 55 was divided by 5 because approximately one-fifth of the 50 to 55 age group turned 51 in 2000.

Surgical menopause. The U.S. hysterectomy surveillance (1994-1999) from the Centers for Disease Control provides estimated overall rates for hysterectomies by age plus percentages for those hysterectomies that included a bilateral oophorectomy. Applying those rates to U.S. Census Bureau data for premenopausal-aged women provides an estimate of the number of women who had undergone a hysterectomy with bilateral oophorectomy before age 50. No overall numbers are published for bilateral oophorectomies without hysterectomy. Given that bilateral oophorectomies without hysterectomy are relatively rare, a conservative estimate was added to round the number up to 2 million.

Data are inconclusive regarding the association of hysterectomy with ovarian failure occurring earlier than normal. Thus, numbers for that group have not been included.

Annual numbers for surgical menopause come from the 2000 National Hospital Discharge Survey. Oophorectomy data for women aged 15 to 44 years plus 25% of women aged 45 to 64 were combined to provide an estimate. The survey also provides data on hysterectomies, but it is not known whether those data included hysterectomies with bilateral oophorectomies.

Premature spontaneous menopause. Several studies, including SWAN, indicate that the percentage of U.S. women experiencing premature spontaneous menopause is approximately 1%. Applying that percentage to women aged 15 to 40 in the 2000 U.S. census gives an estimate of U.S. women who have experienced premature spontaneous menopause. This is the total number of U.S. cases; the annual figure is not known.

Induced menopause from other causes (eg, chemotherapy, pelvic radiation therapy). There are no hard data from which to calculate estimates, so these women are not included.

Canada. Canadian statistics also show an increase in life expectancy for midlife women. In 1922, a 50-year-old woman lived on average until age 75. Today, a woman the same age can expect to live until her mid-80s. Thus, Canadian women are living at least one-third of their lives after menopause. Approximately 4.78 million women (15.4% of the Canadian population) were aged 50 and older in 2001. By 2021, that number is projected to increase to 7.4 million (21% of the Canadian population).

Worldwide. In 1998, there were more than 477 million postmenopausal women in the world, with approximately 9% expected to live to age 80. By 2025, the number of postmenopausal women is expected to rise to 1.1 billion. Life expectancy for women worldwide was 65 years in 1998 (79 in more developed countries). That is expected to rise to 72 years worldwide by 2025 (82 years in more developed countries).

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Evaluating the literature

As new studies are published, the evidence base for understanding the risks and benefits of treatment options changes. A basic understanding of the types of studies and the meaning of the analyses helps healthcare providers evaluate the evidence and implications for clinical practice.

Types of studies. The two major types of studies are *experimental* and *observational*. In experimental studies, the interventions and conditions are strictly defined and controlled. In observational studies, investigators observe outcomes in relation to variables of interest, but they do not assign participants to the study exposure. The most common types of studies are listed here, ordered by the strength of evidence they provide.

Experimental studies. The two types of experimental studies are randomized controlled trials and crossover trials.

- *Randomized controlled trials* are the gold standard of scientific inquiry. In these studies, a group of subjects with similar characteristics is identified. Each subject is then randomly assigned to an intervention or a control group. In this way, the biases of observational studies are avoided because participants have an equal and unbiased (ie, random) chance of being assigned to each treatment under study.

These types of trials are well suited to situations in which exposure to treatment is modifiable, a legitimate uncertainty exists regarding the benefit and/or harm of treatment, and outcomes are reasonably common. However, the selection criteria may limit the generalizability of the results.

Depending on the intervention, both participants and investigators may be blinded (ie, not informed) as to which treatment a participant is receiving. Blinding controls for potential placebo effects and the effects of a participant's expectation of benefit. Randomized controlled trials assess the efficacy of the treatment in a controlled setting, which may not reflect its actual effectiveness in a real-world, clinical-practice setting. Often, the trials use a highly defined patient population, so it may not be accurate to extrapolate the results to other patient populations. The Women's Health Initiative is an example of a randomized controlled trial.

- *Crossover trials* allow subjects to serve as their own controls. Participants are randomly assigned to one treatment arm and later switched to the other treatment arm. The crossover study methodology has often been used in trials to assess efficacy of medications such as in the treatment of vasomotor symptoms.

Observational studies. Types of observational studies include longitudinal cohort studies, case-control studies, case reports, and case series.

- *Cohort studies* begin with a defined group of subjects (eg, individuals of a certain age or who work in a certain industry) called the cohort. This cohort is then followed over time for a variety of outcomes. Most commonly, data are collected in a similar manner on all participating subjects at the beginning of the study (baseline) and at set intervals during follow-up.

The studies provide a clearer temporal sequence of exposures and/or outcomes, are well suited for rare exposures, and can study multiple exposures and/or outcomes. However, they can be time consuming and expensive, have the potential for bias, and may lose participants during follow-up.

Cohort studies are usually prospective, but they may be retrospective (ie, all relevant exposures and events will already have occurred when the study is initiated). Evidence from prospective cohort studies is considered stronger because data on exposures are collected before the outcomes occur. The Nurses' Health Study and the Framingham Study are examples of large, prospective, cohort studies.

- *Case-control studies* most commonly begin with an outcome of interest (eg, myocardial infarction, breast cancer) and then compare the characteristics of individuals with the outcome (cases) and without the outcome (controls). Data are analyzed using a snapshot approach, determining at a single point in time the differences that may account for the outcome.

Matching subjects for specific characteristics and defining strict eligibility criteria lessens, but cannot eliminate, the possibility that the results are caused by bias. For example, women who use estrogen therapy are known to smoke less and be generally healthier, and this biases any observation of estrogen therapy and health outcomes.

Despite these limitations, case-control studies have many advantages. Because they begin with an outcome of interest, they can be performed efficiently and at less cost than cohort studies. They are important in situations in which it would be unethical to assign individuals to an exposure (eg, asbestos) or when an outcome is relatively rare so that the number of identified cases in any given cohort would be too small to analyze (eg, birth defects).

- *In case reports and case series*, the experience of a single patient or series of patients is described. Such reports are useful in bringing new diseases or phenomena to the attention of the clinical and scientific community and for generating new hypotheses. However, without further study, case reports can be considered only suggestive.

Analyses. The results of epidemiologic studies and clinical trials are frequently presented as a relative risk (RR)(see Table 2).

Table 2. Relative risk nomenclature

The RR tells the estimated magnitude of the change in risk related to the presence versus the absence of a factor of interest.

An RR *less than* 1.0 is associated with lower risk. For example, an RR of 0.50 means that there is a 50% reduction in risk among those with versus those without the factor. An RR of 0.3 means a 70% reduction in risk.

An RR *greater than* 1.0 means that the factor increases risk. For example, an RR of 1.2 means that there is a 20% increase in risk in the group with versus those without the factor. An RR of 2.0 means a doubling of risk.

The *P value* is the probability of obtaining the observed RR (or a more extreme value) by chance.

The *confidence interval* (CI), usually cited with the RR, indicates with a certain degree of assurance the range within which the true magnitude of the measured effect lies. A 95% CI gives the range of values that have a 95% probability of containing the true RR. When a 95% CI does not contain the number 1.0 (eg, 0.40-0.80 or 1.12-1.37), the measured RR is significant by at least $P < 0.05$. A wide CI reflects a wide variation in the data.

The *odds ratio* is an estimate used in case-control studies that approximates the RR.

The RR is the rate of disease in a group exposed to a potential risk factor, divided by the rate of disease in the unexposed group. For example, if the annual rate of myocardial infarction in women who smoke is 220 per 100,000 and the annual rate in women who do not smoke is 110 per 100,000, the RR associated with smoking would be determined as follows:

$$RR = \frac{220}{100,000/\text{year}} \div \frac{110}{100,000/\text{year}} = 2.00$$

This means that compared with unexposed women, the rate of myocardial infarction for smoking women is twice that of nonsmoking women.

The impact of RR depends on incidence. This can be quantified by *attributable risk* (AR; or risk difference). This is the difference in the incidence rates in the exposed and unexposed groups (the groups with and without the risk factor being studied). The AR serves to quantify the effect of exposure and thus gives a measure of its public health impact. For example, in the calculation presented earlier, the AR would be as follows:

$$AR = \frac{220}{100,000/\text{year}} - \frac{110}{100,000/\text{year}} = \frac{110}{100,000/\text{year}}$$

This means that for every 100,000 women who smoke, there would be 110 additional cases of myocardial infarctions per year. Depending on the baseline rates of disease, the AR can vary greatly, given the same RR. For example, if the baseline rate of a disease is 6 per 100,000 per year and smoking doubled the risk to 12 per 100,000 per year, the RR would be 2.0; however, the AR would be only 6 per 100,000 per year.

A *meta-analysis* is an analytic technique used to pool the results from many smaller studies. Pooling studies has the effect of increasing the sample size, thereby gaining statistical power. Thus, a meta-analysis may pool the results of clinical trials that are too small to have statistical significance in themselves but that may show significance when pooled. Specific criteria (eg, eligibility criteria of subjects, data completeness) are established to determine which studies will be included in the analysis. Observational studies may also be pooled in a meta-analysis. It must be remembered that any biases present in the contributing studies will be present in the meta-analysis.

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