

Menopause is a natural event for most women, occurring at around age 51. The usual range is 45 to 55 years. However, some women experience menopause earlier than usual. Ovarian insufficiency resulting in premature menopause is thought to affect approximately 1% of reproductive-age women in North America (approximately 0.1% before age 30). Most women with this diagnosis have remaining primordial follicles that do not adequately respond to gonadotropin stimulation. Those follicles, however, may still function sufficiently to produce estradiol. Ovulation (and thus potential pregnancy) may occur intermittently and unpredictably for years. Although menopausal hormone therapy (HT), either estrogen alone or with progesterone, is often prescribed to augment folliculogenesis, no treatment has proven effective in restoring fertility.

Premature menopause is a general term used to describe menopause that occurs at or before age 40. This can happen either naturally (spontaneously) or it can be induced through medical interventions (bilateral oophorectomy or ovarian damage from chemotherapy or pelvic radiation therapy).

The younger a woman is when she experiences menopause, the longer she is without reproductive-age levels of endogenous estrogen. This increases her risk for symptoms and diseases associated with low estrogen levels compared with women who reach menopause at the typical age. Menopause symptoms, the possible effects on sexual function and mental health, and prevention of osteoporosis and heart disease should be discussed.

Premature ovarian failure (POF) describes ovarian insufficiency leading to amenorrhea in women before age 40. Although most cases are permanent, POF can be transient. When POF is permanent, the term “premature menopause” applies.

Some cases of premature ovarian insufficiency or POF lead to temporary amenorrhea. Women who overexercise or overdiet may experience amenorrhea due to a hypoestrogenic state, which is a typical premature secondary ovarian insufficiency as the problem is due to hypothalamic dysfunctions. Some women experience temporary amenorrhea after chemotherapy or pelvic radiation therapy. Certain drug therapies, such as gonadotropin-releasing hormone (GnRH) analogues—which inhibit secretion of gonadotropins by blocking GnRH receptors at the pituitary, causing the ovaries to temporarily stop hormone production, inducing a hypoestrogenic state—may also result in temporary amenorrhea.

Natural premature menopause

This section reviews the causes, evaluation, symptoms, and management of natural premature menopause.

Causes. It is estimated that between 5% and 25% of women with idiopathic or presumed autoimmune POF will experience at least one spontaneous remission. Among

women with POF who have a normal karyotype, one half may still have ovarian follicles capable of functioning intermittently.

Because the ovaries of women with POF fail to function adequately in response to appropriate endogenous gonadotropin stimulation, the condition is also known as “primary ovarian insufficiency.” In contrast, “secondary ovarian insufficiency” refers to the failure of the hypothalamus and pituitary glands to produce appropriate gonadotropin stimulation.

Two thirds of cases of POF are idiopathic. Known causes are listed below in Table 1.

Table 1. Known causes of premature ovarian failure

Karyotype abnormality
Pure gonadal dysgenesis
Iatrogenic treatments
Autoimmune disorders
• Polyglandular
• Immunoglobulin G, immunoglobulin A
Miscellaneous disorders
• Enzyme deficiency
• Metabolic syndromes
• Pseudohypoparathyroidism
• Thymic disorders
Pseudo causes
• Gonadotropin-producing pituitary adenoma
• Hypothyroidism
• Isolated gonadotropin deficiency

Familial clusters of POF clearly exist. In a large Italian study, early ovarian failure had a recognizable heritable association in nearly one third of the women evaluated. Although genetic or familial factors may influence ovarian aging, the prevalence of these factors, the relative expression, and the proportion of early ovarian failure attributed to genetic or familial causes are not known.

The gene locus on the X chromosome is related to ovarian failure. Women with a single X chromosome, such as those with Turner's syndrome, develop normal ovaries with a normal complement of primordial follicles. They experience accelerated atresia (degeneration of ovarian follicles) that often leads to ovarian failure. Most women with galactosemia (an autosomal-recessive condition) eventually develop POF, along with hepatocellular damage, renal cellular damage, the development of cataracts, and mental retardation.

Uterine artery embolization for symptomatic uterine fibroids is another possible cause of earlier ovarian failure with an iatrogenic basis. Women undergoing this procedure