TABLE 412-4 DIFFERENTIAL DIAGNOSIS OF DELAYED PUBERTY

Hypergonadotropic
Ovarian
Turner's syndrome
Gonadal dysgenesis
Chemotherapy/radiation therapy
Galactosemia
Autoimmune oophoritis
Congenital lipoid hyperplasia
Steroidogenic enzyme abnormalities
17α-Hydroxylase deficiency
Aromatase deficiency
Gonadotropin/receptor mutations
FSHβ, LHR, FSHR
Androgen resistance syndrome
Hypogonadotropic
Genetic
Hypothalamic syndromes
Leptin/leptin receptor
HESX1 (septo-optic dysplasia)
PC1 (prohormone convertase)
IHH and Kallmann's syndrome
KAL1, FGF8, FGFR1, NSMF, PROK2, PROKR2,
KISS1, KISS1R, TAC3, TAC3R, GnRH1, GnRHR, SEM3A, HS6ST1, WDR11, CHD7
Abnormalities of pituitary development/function
PROP1
CNS tumors/infiltrative disorders
Craniopharyngioma
Astrocytoma, germinoma, glioma
Prolactinomas, other pituitary tumors
Histiocytosis X
Chemotherapy/radiation
Functional
Chronic diseases
Malnutrition
Excessive exercise
Eating disorders

Abbreviations: *CHD7*, chromodomain-helicase-DNA-binding protein 7; CNS, central nervous system; *FGF8*, fibroblast growth factor 8; *FGFR1*, fibroblast growth factor 1 receptor; *FSHβ*, follicle-stimulating hormone β chain; *FSHR*, FSH receptor; *GNRHR*, gonadotropin-releasing hormone receptor; *HESX1*, homeobox, embryonic stem cell expressed 1; *HS6ST1*, heparin sulfate 6-O sulfotransferase 1; IHH, idiopathic hypogonadotropic hypogonadism; KAL, Kallmann; *KISS1*, kisspeptin 1; *KISSR1*, KISS1 receptor; *LHR*, luteinizing hormone receptor; *NSMF*, NMDA receptor synaptonuclear signaling and neuronal migration factor; *PROK2*, prokineticin 2; *PROKR2* prokineticin receptor 2; *PROP1*, prophet of Pit1, paired-like homeodomain transcription factor *SEMA3A*, semaphorin-3A; *WDR11*, WD repeat-containing protein 11.

413 Menopause and Postmenopausal Hormone Therapy

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Menopause is the permanent cessation of menstruation due to loss of ovarian follicular function. It is diagnosed retrospectively after 12 months of amenorrhea. The average age at menopause is 51 years among U.S. women. *Perimenopause* refers to the time period preceding menopause, when fertility wanes and menstrual cycle irregularity increases, until the first year after cessation of menses. The onset of perimenopause precedes the final menses by 2–8 years, with a mean duration of 4 years. Smoking accelerates the menopausal transition by 2 years.

Although the peri- and postmenopausal transitions share many symptoms, the physiology and clinical management of the two differ. Low-dose oral contraceptives have become a therapeutic mainstay in perimenopause, whereas postmenopausal hormone therapy (HT) has been a common method of symptom alleviation after menstruation ceases.

PERIMENOPAUSE

PHYSIOLOGY

Ovarian mass and fertility decline sharply after age 35 and even more precipitously during perimenopause; depletion of primary follicles, a process that begins before birth, occurs steadily until menopause (Chap. 412). In perimenopause, intermenstrual intervals shorten significantly (typically by 3 days) as a result of an accelerated follicular phase. Follicle-stimulating hormone (FSH) levels rise because of altered folliculogenesis and reduced inhibin secretion. In contrast to the consistently high FSH and low estradiol levels seen in menopause, perimenopause is characterized by "irregularly irregular" hormone levels. The propensity for anovulatory cycles can produce a hyperestrogenic, hypoprogestagenic environment that may account for the increased incidence of endometrial hyperplasia or carcinoma, uterine polyps, and leiomyoma observed among women of perimenopausal age. Mean serum levels of selected ovarian and pituitary hormones during the menopausal transition are shown in Fig. 413-1. With transition into menopause, estradiol levels fall markedly, whereas estrone levels are relatively preserved, a pattern reflecting peripheral aromatization of adrenal and ovarian androgens. Levels of FSH increase more than those of luteinizing hormone, presumably because of the loss of inhibin as well as estrogen feedback.

DIAGNOSTIC TESTS

The Stages of Reproductive Aging Workshop +10 (STRAW+10) classification provides a comprehensive framework for the clinical assessment of ovarian aging. As shown in Fig. 413-2, menstrual cycle characteristics are the principal criteria for characterizing the menopausal transition, with biomarker measures as supportive criteria. Because of their extreme intraindividual variability, FSH and estradiol levels are imperfect diagnostic indicators of perimenopause in menstruating women. However, a consistently low FSH level in the early follicular phase (days 2–5) of the menstrual cycle does not support a diagnosis of perimenopause, while levels >25 IU/L in a random blood sample are characteristic of the late menopause transition. FSH measurement can also aid in assessing fertility; levels of <20 IU/L, 20 to <30 IU/L, and ≥30 IU/L measured on day 3 of the cycle indicate a good, fair, and poor likelihood of achieving pregnancy, respectively. Antimüllerian hormone and inhibin B may also be useful for assessing reproductive aging.

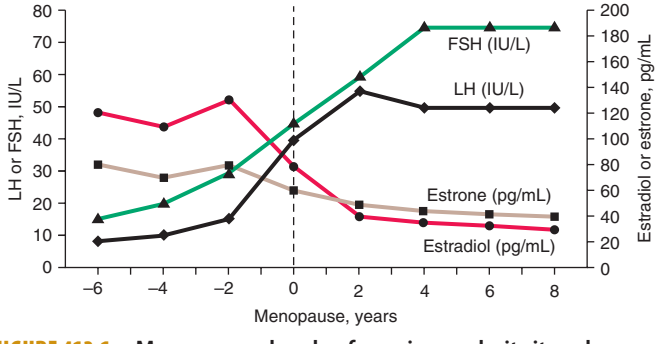

FIGURE 413-1 Mean serum levels of ovarian and pituitary hormones during the menopausal transition. FSH, follicle-stimulating hormone; LH, luteinizing hormone. *(From JL Shifren, I Schiff: J Womens Health Gend Based Med 9 Suppl 1:S3, 2000.)*