Premature Menopause

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KEYWORDS

- Premature menopause • Primary ovarian insufficiency • Premature ovarian failure
- Hypergonadotropic hypogonadism • Surgical menopause

KEY POINTS

- Women of reproductive age who experience loss of menstrual regularity for 3 or more consecutive months should have an evaluation for primary ovarian insufficiency (POI) at the time of the first visit.
- Two elevated levels of gonadotropins (>20 IU/L) with low estradiol levels on 2 occasions, at least 4 to 6 weeks apart, are consistent with a diagnosis of POI.
- Because of the potential detrimental long-term health implications of estrogen deprivation, prompt diagnosis and treatment by health care providers is of utmost importance.
- A multidisciplinary team approach is ideal for managing women diagnosed with POI, given the complexity and sensitive nature of the disorder.

INTRODUCTION

Cessation or loss of ovarian function before age 40 years is considered "premature," an age threshold that is 2 standard deviations below the mean estimated age of menopause (50 ± 4 years) seen in the reference population.[1] Premature menopause may be spontaneous or induced, for example, following chemotherapy, radiation, or surgical removal of the gonads.

Spontaneous premature menopause is not uncommon; it is estimated that approximately 0.3% to 1.1% of reproductive-age women experience menopause prematurely.[2] Among women younger than 40, the incidence increases with advancing age; premature menopause may be recognized in 0.01% of women younger than 20, 0.1% of those younger than 30, and approximately 1% of women younger than 40 years.[3] Premature menopause, primary ovarian insufficiency (POI), and premature ovarian failure (POF)

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are terms that are often used interchangeably. Given that premature cessation of ovarian function, either spontaneous or following iatrogenic insult other than castration, may not be "permanent," and keeping in perspective the negative connotation implied by the term "failure," POI has emerged in recent years as the preferred terminology. Spontaneous premature menopause is henceforth referred to as POI.

SYMPTOMS

By definition, cessation of menstrual function for longer than 1 year in an appropriate clinical setting defines menopause; however, shorter durations of amenorrhea are equally meaningful in the context of POI. Although primary amenorrhea may be the presenting symptom in up to 10% of cases, in most cases POI manifests after attainment of normal pubertal development and after the establishment of regular menses.[4] Occasionally, secondary amenorrhea following a pregnancy or cessation of hormonal contraceptive regimen may be the first presenting sign of POI. Persistent elevation in circulating gonadotropins with concomitant hypoestrogenemia is the endocrine hallmark of ovarian failure. Documented elevation in circulating gonadotropins along with low estradiol levels detectable on 2 occasions, at least 4 to 6 weeks apart, is required before labeling a reproductive-age woman with the diagnosis of POI in the context of infrequent or absent menses.[4–7]

Menstrual irregularities may also be accompanied with constant or intermittent hypoestrogenic symptoms that define the menopausal syndrome, such as hot flashes, night sweats, emotional lability, vaginal dryness, or sleep disturbances. Notable, however, is the absence of menopausal symptoms in the setting of primary amenorrhea; namely, these symptoms are uncommon in those who were never exposed to estrogen.[8] Concerns relating to subfertility may be yet another presenting symptom. The clinical presentation of POI can thus vary from woman to woman.

DIAGNOSTIC EVALUATION AND TESTS

A thorough review of the woman's medical history, including family history, may offer critical insights leading to the diagnosis. Of particular relevance are details regarding menstrual history, including age at menarche and pattern of menses. Any prior medication or treatment that may have caused gonadal impairment must be documented. In addition, the history should focus on the presence or absence of nonreproductive endocrinopathies, including hypothyroidism, hypoadrenalism, and hypoparathyroidism. Furthermore, any family history of POI, mental retardation, particularly in male progeny (see fragile X mental retardation 1 [FMR1] in the section Differential Diagnoses), or chromosomal abnormalities should be noted.

Diagnosis of POI is commonly delayed despite a manifest clinical picture, partly because of the relative infrequency of this entity. Furthermore, POI is often misdiagnosed and improperly managed because of lack of familiarity with this disorder by health care providers. Thus, the first challenge is to arrive at the diagnosis in a timely fashion. Definitive diagnostic criteria have not been delineated. The challenge lies in deciding how long to wait before initiating investigations into the loss of menstrual regularity in a young woman. Loss of regular menses for more than 3 consecutive months merits further investigation, and POI should be considered among the differential diagnoses.

Physical Evaluation

Careful attention should be placed on the presence or absence of secondary sex characteristics, particularly in the setting of primary amenorrhea. Although most patients

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