Chapter 30
Premature Ovarian Failure

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Objective

To review the diagnosis, diagnostic workup, and long-term follow-up of women with premature ovarian failure.

Case Presentation

A 31-year-old woman presented with a 2-year history of infertility. She underwent menarche at the age of 12 years and had regular cycles with intermittent development of ovarian cysts. The cysts were treated with oral contraceptive pills (OCPs) from age 24 to 26 years. She became amenorrheic after discontinuing the OCPs 5 years ago. She denied headaches, visual field loss, excessive hair growth or acne, galactorrhea, and hypo- or hyperthyroid symptoms. She did low-impact aerobics and denied eating disorders. She noted very occasional hot flashes. Her past medical history was remarkable for hypothyroidism, diagnosed at age 11 years, for which she took thyroid hormone replacement. Her family history was unremarkable. She did not smoke cigarettes and worked as a lawyer. On physical exam she was not orthostatic; height was 156 cm, weight was 47.3 kg, and body mass index (BMI) was 19 kg/m$^2$. She had no vitiligo, hirsutism, acne, or acanthosis, normal peripheral visual fields, a 10-g thyroid, no galactorrhea, and slightly enlarged ovaries.

Her laboratory evaluation demonstrated a thyroid-stimulating hormone (TSH) of 2.27 mU/L (normal 0.5–5), prolactin 12.8 µg/L (normal 0–15), β-human chorionic gonadotropin (HCG) negative, and follicle-stimulating hormone (FSH) 19.9 IU/L (postmenopausal >30 IU/L; 1 standard deviation [SD] above the mean for normal women, 15 IU/L) and estradiol <20 pg/mL. An inhibin B level was very high at 1000 pg/mL (normal follicular phase average 173 pg/mL). An ultrasound demonstrated multiple ovarian cysts bilaterally (1 of 10 mm, 3 of 12 mm, and one each at...
Magnetic resonance imaging (MRI) demonstrated a normal pituitary gland.

The patient underwent several cycles of ovulation induction using a combination of purified luteinizing hormone (LH) and FSH. Although she grew two to three dominant follicles with each treatment, she had very low estradiol levels and did not become pregnant. After three cycles of treatment she was again amenorrheic, and a repeat FSH level reached the postmenopausal range. An ultrasound performed at the same time demonstrated inactive ovaries. Antiadrenal antibody testing was negative. Fragile X premutation testing and a karyotype were normal. The patient was treated with estradiol and cyclic progesterone for hormone replacement. She and her husband adopted two children.

The patient subsequently developed achy joints and a positive antinuclear antibody with a homogeneous, 1:160 titer. Ten years later, the patient developed darkening of the skin and extreme fatigue. A Cortrosyn stimulation test demonstrated baseline cortisol 108 nmol/L, which was unchanged 1 hour after 0.25 mg Cortrosyn. Adrenocorticotropic hormone (ACTH) was elevated at 176 pmol/L. She was treated with prednisone and fludrocortisone.

**How the Diagnosis Was Made**

Premature ovarian failure is the diagnosis given to women under age 40, with amenorrhea, elevated gonadotropin levels, and low estradiol. It can present as primary amenorrhea and failure to go through puberty, as in Turner’s syndrome, or as secondary amenorrhea. Symptoms include hot flashes, insomnia, worsening premenstrual syndrome, and night sweats, as seen in this patient. The FSH level is typically elevated into the postmenopausal range.

Despite its name, premature ovarian failure is characterized by intermittent follicle development and ovulation that can occur even after several months of amenorrhea. During these times of intermittent follicle development, which can be detected on ultrasound, the FSH may be in the normal range due to negative feedback from estradiol or inhibin B. In this case, the patient’s FSH level did not reach the postmenopausal range initially, but was greater than 1 SD above the mean for reproductive aged women on day 3 of the menstrual cycle with a very low estradiol but a high inhibin B. There is evidence that an FSH level 1 SD above the mean for normal women on menstrual cycles days 2 to 4 indicates reduced fertility during assisted reproductive technology treatments, even when menstrual cycles are still regular. As illustrated in the patient’s follow-up course, such a pattern may represent an early presentation of ovarian failure. Unfortunately, the prognosis for fertility is quite low with a relatively elevated FSH level whether there is intermittent follicular development and normalization of FSH or even regular menstrual cycles.

The FSH should be repeated for confirmation before a diagnosis of premature ovarian failure is given to a patient, keeping in mind that intermittent follicular development can transiently normalize the FSH level. It is important to remember