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An update: spontaneous premature ovarian failure is not an early menopause

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Objective: To update clinicians regarding the management of women with spontaneous premature ovarian failure (POF).
Design: Literature review and consensus building among three clinicians with experience in caring for women with spontaneous POF.
Conclusion(s): Clearly the ovarian "failure" in this disorder is not permanent in all women. Approximately 5%–10% may conceive spontaneously and unexpectedly after the diagnosis. An integrated approach to management is best, and there is a need to first address physical and mental health issues before addressing plans for family building. Women with spontaneous POF are at increased risk of adrenal insufficiency, which should be detected and managed appropriately, especially before proceeding to ovum or embryo donation procedures. Young women with POF experience pathologically low serum E_2 levels at least intermittently. Despite the absence of controlled evidence for this specific population, physiologic *replacement* of ovarian steroid hormones seems rational until the age of normal menopause. The disorder may be associated with other conditions that require evaluation and management, including hypothyroidism, dry eye syndrome, abnormal karyotype, or a premutation of the FMR1 gene. Finally, clinicians need to be sensitive to the emotional aspects of this disorder when delivering the diagnosis and during subsequent management. (Fertil Steril® 2005;83:1327–32. ©2005 by American Society for Reproductive Medicine.)

Key Words: Premature ovarian failure, premature menopause, hypergonadotropic amenorrhea, hypergonadotropic hypergonadism, ovarian insufficiency, autoimmune oophoritis, estrogen, hormone replacement, adrenal insufficiency, hypothyroidism, FMR1, fragile X syndrome

Premature ovarian failure (POF) is a mysterious disorder. It is not even clear that this is the best term to describe the condition. Other terms that have been used are premature menopause, hypergonadotropic amenorrhea, hypergonadotropic hypogonadism, and ovarian insufficiency. Women with POF bring important questions to the clinician that need to be addressed.

This discussion will focus on spontaneous POF, meaning the condition was not induced by chemotherapy, radiation, or surgery. The loss of endocrine ovarian function that occurs with POF has systemic effects and the associated loss of fertility can have profound emotional effects. An integrated approach to management that first addresses physical and mental health issues before addressing plans for family building is best.

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IS THIS PREMATURE MENOPAUSE?

Menopause is defined as "permanent cessation of menses; termination of the menstrual life" (1). It normally occurs at an average age of 50 years. Formerly known as premature menopause, the disorder "POF" now generally describes a syndrome consisting of amenorrhea, elevated menopausal level gonadotropins, and sex steroid (i.e., estrogen [E]) deficiency in women less than 40 years old (2).

At one time it was believed that an FSH level in the menopausal range was prima facie evidence of ovarian follicle depletion, equivalent to irreversible and permanent cessation of ovarian function (3), resulting in use of the term premature menopause. It has become clear that this is not the case (4). We now know that ovarian "failure" does not mean permanent cessation of ovarian function. Rather, approximately 50% of young women with this condition experience

intermittent and unpredictable ovarian function that can continue for many years (4–8).

In one report a woman resumed cyclic ovulation after 8 years of amenorrhea (4). Spontaneous pregnancies can even occur subsequent to the diagnosis in about 5%–10% of these women, sometimes many years later (9). In those women who have follicles remaining in the ovary, in most cases the follicles fail to function normally due to inappropriate luteinization (6).

Definitive criteria on which to establish a diagnosis of POF have not been delineated, although an operational definition in common use is at least 4 months of amenorrhea in association with menopausal level serum FSH concentrations on two occasions (5, 10, 11). Clearly the fallacy of using elevated FSH levels alone to make a diagnosis of irreversible ovarian failure has been established, and the same is true even for women who have experienced 4 months of amenorrhea and menopausal symptoms as well (5, 6).

Thus, the term POF is medically inaccurate, misleading to patients, and for many patients both offensive and psychologically hurtful. The term hypergonadotropic amenorrhea is more accurate, although patients can have severely impaired ovarian function without experiencing 4 months of complete amenorrhea. The term hypergonadotropic hypogonadism is more accurate still, but this term is a mouthful for patients and clinicians. "Ovarian insufficiency," used in the French literature, may be better (12).

The term ovarian insufficiency communicates a sense that the pathophysiology represents a continuum. Also, the term may be more acceptable to patients in that it reflects some measure of hope with regard to spontaneous remission and subsequent pregnancy. To facilitate clinical research and communication regarding patient care for this disorder there is a need to delineate standardized diagnostic criteria and terminology. Because ovarian insufficiency is in reality a continuum, it seems logical that some sort of staging system should be developed.

MAKING THE DIAGNOSIS

The first challenge is to make the diagnosis of POF in a timely manner. One report found that more than 50% of patients who presented with secondary amenorrhea saw three or more different clinicians before laboratory testing was performed to make this diagnosis (13). A complete discussion regarding the differential diagnosis of secondary amenorrhea is beyond the scope of this review. Young women who experience loss of menstrual regularity for 3 or more consecutive months deserve appropriate evaluation at their first visit to a clinician (14).

In general, at a minimum, initial evaluation of amenorrhea will include measurement of serum prolactin, FSH, and thyroid-stimulating hormone (TSH) (after pregnancy is ruled out). If FSH is in the menopausal range in a woman less than 40 years of age, the test should be repeated, along with measurement of serum E_2 to confirm hypogonadism. There is no need to use the progestin-withdrawal test as a substitute for measuring serum FSH and E_2 levels. In fact, the progestin-withdrawal test may be misleading because of intermittent ovarian function. One-half of women with POF will respond to the progestin challenge, and the appropriate diagnosis will be delayed (4). Many of these patients withdraw to progestin because the hypoestrogenism may be only intermittent.

The second challenge is to inform the patient about the diagnosis in a sensitive manner. Many women describe feeling emotionally devastated after the diagnosis of POF. The manner in which the diagnosis is delivered can impact the degree of emotional trauma experienced. Thus, a carefully planned, sensitive approach is required when informing patients of this diagnosis.

It is best to schedule a return visit to the office to review the laboratory results and treatment options when this diagnosis is suspected. It is also important to explain that remissions and spontaneous pregnancies can occur, and that POF differs from the normal menopause in important ways. Scheduling sufficient time to go over the medical and emotional impact of the diagnosis is essential.

DEFINING THE ETIOLOGY

When ovarian failure presents as primary amenorrhea, approximately 50% will be associated with an abnormal karyotype (4). However, most cases of spontaneous POF present as secondary amenorrhea. One series found an abnormal karyotype in only 13% of a select group of younger women who developed secondary amenorrhea due to POF (at age 30 years or less) (4). Thus, in most cases the diagnosis will be 46,XX spontaneous POF, meaning the karyotype is normal.

In 90% of cases no etiology for spontaneous POF will be identified, even after a thorough evaluation. Approximately 4% of women with 46,XX spontaneous POF will have steroidogenic cell autoimmunity as the mechanism of POF (15, 16).

Approximately 6% of women with 46,XX spontaneous POF will have premutations in the FMR1 gene (17, 18). This is the gene responsible for fragile X syndrome, the most common cause of familial mental retardation. The risk of having an FMR1 premutation is higher if there is a family history of POF (17, 18).

It is critical to take a family history. Women who have relatives with spontaneous POF should be referred for genetic counseling. Furthermore, a family history of either fragile X syndrome, unexplained mental retardation, dementia, a child with developmental delay, or a tremor/ataxia syndrome is reason for genetic counseling. It is now known that premutations in the FMR1 gene, once thought to be an