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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

asymptomatic carrier state, can be associated with a neurodegenerative disorder (19, 20).

Specific genetic testing for the FMR1 gene is clinically available. Approximately 14% of women with familial POF will have a premutation in the FMR1 gene as compared with 2% of women with isolated POF (18). Women found to have a premutation in the FMR1 gene are at risk of having a child with mental retardation, should they be one of the 5%–10% who conceive.

For women with sporadic spontaneous POF, no analysis of the cost/benefit or ethical, legal, or social implications of such testing is available to inform what constitutes appropriate genetic evaluation. Referring these patients to a research group that is funded to study the genetics of POF is a possible solution. There are other rare genetic causes of familial POF for which routine genetic testing in sporadic cases is now not clinically indicated, such as mutations involving FSHR (FSH receptor), GALT (galactose-1-phosphate uridylytransferase associated with galactosemia), FOXL2 (a forkhead transcription factor associated with the blepharophimosis/ptosis/epicantus inversus syndrome), INHA (inhibin alpha gene), EIF2B (a family of genes associated with central nervous system leukodystrophy and ovarian failure), BMP15 (bone morphogenetic protein 15), and AIRE (autoimmune regulator gene associated with the autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome) (21–31).

Autoimmune lymphocytic oophoritis, the mechanism of the ovarian failure in steroidogenic cell autoimmunity, was originally reported in association with adrenal insufficiency (Addison disease) (15, 32). It is important to identify the small subset of women presenting with POF who have associated steroidogenic cell autoimmunity. This can be accomplished by testing for adrenal antibodies using an indirect immunofluorescence assay (the test is commercially available).

One review reported that all patients with histologically confirmed lymphocytic autoimmune oophoritis had adrenal antibodies detected (when tested) (15). There is evidence also that 21-hydroxylase antibodies measured by an immunoprecipitation assay is generally in good agreement with results testing for adrenal cortex antibodies by indirect immunofluorescence, although a variety of antibodies to steroidogenic enzymes can be detected in patients with steroidogenic cell autoimmunity (33). Testing for adrenal antibodies by indirect immunofluorescence will identify the 4% of women with spontaneous POF who have steroidogenic cell autoimmunity and are at risk of adrenal insufficiency, a potentially fatal disorder (16, 34, 35). Presently there is no test to detect ovarian-specific antibodies that has any proven clinical utility (36, 37).

When POF and adrenal insufficiency occur together the ovarian failure presents first in 9 of 10 cases (38). A few women, about 2%, will have asymptomatic adrenal insufficiency when they initially present with spontaneous POF, and will be at risk of developing adrenal crisis. It is critical to identify women with adrenal insufficiency before proceeding to egg donation. Untreated adrenal insufficiency during pregnancy is associated with a high incidence of serious fetal and maternal complications, such as fetal death in utero and postpartum adrenal crisis (39).

Adrenal antibody testing not only detects women who may have occult adrenal insufficiency at the time of their initial presentation, but also identifies women who should be followed closely for the subsequent development of adrenal insufficiency (40, 41). Screening by measuring a morning serum cortisol level in this population has been shown to have low sensitivity and specificity (16). Also, the ACTH stimulation test was developed as a diagnostic test, not as a screening test.

When used as a screening test, the ACTH stimulation test has a false-positive rate nearly the same as the frequency of adrenal insufficiency in this population (upper 95% confidence limit is 5%) (16). Therefore, the ACTH stimulation test should be reserved as a diagnostic test for women with symptoms of adrenal insufficiency or with positive adrenal antibodies. Women with positive adrenal antibodies will require referral to a medical endocrinologist for additional evaluation and long-term follow-up of their adrenal function. There is a need for longitudinal studies to better assess the natural history of adrenal function in women who present with spontaneous POF.

MANAGING THE PATIENT

Health can be defined as a complete state of physical, mental, spiritual, and social well-being. The diagnosis of POF can have effects on all of these aspects of health. Here our discussion is limited to the health implications for women with 46,XX spontaneous POF. Women found to have an abnormal karyotype or a premutation in the FMR1 gene have additional health implications that are beyond the scope of this discussion.

Emotional Health

Most women want guidance on how to cope with the emotional sequelae of this diagnosis, but few ask for it directly. It is important for clinicians to lead the way on this. A simple statement such as "many patients with POF feel that this is a very difficult diagnosis to accept emotionally" can be an effective entrée into this discussion. Also, helping patients identify individuals with whom they feel comfortable discussing the emotional aspects of this diagnosis and sources of emotional support facilitates needed dialogue.

An association between POF and psychological distress has been reported, and it has been suggested that psychological care should be included in its management (42). Hearing the news of the diagnosis has been described as similar to learning about a death in the family. These feelings of loss

and grief, combined with the disturbed sleep and other physical symptoms of E deficiency, create a special set of needs. Feelings of anger, sadness, guilt, and shame can be overwhelming as patients realize the implications of the diagnosis and the impact on fertility.

Young women are emotionally unprepared for the diagnosis of POF, and this is understandable. Even women who experience natural menopause in their 50s, and are thus afforded a period of adjustment to an anticipated natural physiologic event, often grapple with emotional issues related to the end of fertility, body image, sexuality, aging, and the long-term health implications of the associated E deficiency. As with any life-altering diagnosis, patients with spontaneous POF may experience a sense of loss of control and helplessness, and clinicians can play a key role in alleviating this.

It is important to refer patients to additional accurate sources of information and to assess the strength of their current social support network. Most women with POF benefit from meeting other women with the condition; therefore referral to an organization such as the POF Support Group can be helpful (http://pofsupport.org). Also, many women will benefit from a baseline evaluation with a professional counselor to assess level of depression, anxiety, and coping abilities. It is important to evaluate the POF in the context of other issues the patient may be encountering in her life. In some cases ongoing group or individual therapy is needed, and in some cases psychotropic medication may prove beneficial.

Estrogen Deficiency

Women with POF experience intermittent symptoms of menopause including vasomotor symptoms, sleep disturbance, and vaginal dryness. They appear to be at increased risk for developing osteoporosis and cardiovascular disease despite the sometimes intermittent hypoestrogenism (43–46). Due to recent reports many women with spontaneous POF have significant fears about E therapy.

It is not scientifically valid to apply results of the Women's Health Initiative, a study of older menopausal women, to young women with POF. Young women with POF experience pathologically low serum E_2 levels compared to their peers who have normal ovarian function. Our clinical judgment suggests that remaining sex steroid deficient as a young woman carries a greater long-term health risk than does replacing the hormones normally supplied by the ovaries.

For young women with POF hormonal therapy is truly *replacing* ovarian hormones, just as treatment for juvenile diabetes replaces insulin. At age 50 years or so, these women join the ranks of normally menopausal women and can then be managed as such. In sum, the risk/benefit analysis for *extending* ovarian hormone therapy for normally menopausal women differs from that for *replacing* ovarian hormones in young women with POF, and this needs to be clarified for patients. Because these women are at increased risk for osteoporosis, they should be also be advised regarding calcium intake (1,200–1,500 mg/d), daily weight bearing exercise, and the need to take a daily multivitamin to avoid vitamin D deficiency.

There are no controlled studies regarding the ideal hormone replacement strategy for young women with spontaneous POF. There is room for individualization. Most women do well using a 100-μg E_2 transdermal patch, which averts the first-pass effect on the liver and can be considered full-dose physiologic replacement for young women. On average this achieves a serum E_2 level of 100 pg/mL, near the normal mean E_2 level for normally cycling women of 104 pg/mL (47, 48). Oral E can be given to women who prefer this route of administration.

Typically, about twice as much E as is required for postmenopausal women is needed to alleviate symptoms (100-μg E_2 patch, 2 mg daily dose of oral micronized E_2, or 1.25 mg of conjugated equine E). Cyclic medroxyprogesterone acetate (MPA; 10 mg/d) or oral micronized P (200 mg/d) for 12 days each month should be given to induce regular monthly withdrawal bleeding. Progestin withdrawal less frequently than each month has been associated with the development of endometrial hyperplasia in older women (49). A case can be made for providing a 10-mg dose of MPA or equivalent to fully induce a secretory pattern (50, 51). Lower doses may reduce side effects but require monitoring. Still some patients may prefer a less frequent progestin withdrawal with appropriate monitoring.

If a menstrual period is late, a pregnancy test should be performed and the therapy stopped if positive. Generally oral contraceptives (OC) are not recommended as hormone replacement in spontaneous POF because these preparations contain more steroid hormone than is required for physiologic replacement. Furthermore, women who wish to avoid pregnancy should use a barrier method because the OC is not reliable in women with this disorder, perhaps due to the elevated gonadotropin levels in this condition.

Hypothyroidism

Patients with spontaneous POF may have associated autoimmune disorders (52). Approximately 20% of women with spontaneous POF develop autoimmune hypothyroidism (53). When the diagnosis of POF is made, one should measure TSH and free T_4 and check for the presence of serum thyroid peroxidase autoantibodies.

Adrenal Insufficiency

As noted, approximately 4% of women with spontaneous POF will test positive for adrenal antibodies and are at increased risk of developing autoimmune adrenal insufficiency, a potentially fatal disorder (16). Young women with POF who have not been adequately screened regarding adrenal function are at risk of subsequently developing an

acute adrenal crisis and complications of pregnancy should they conceive (39, 53).

Androgen Insufficiency

As a group, women with POF are androgen deficient, but the clinical significance of this is not clear (54–56). More research is needed regarding androgen replacement in these women.

Dry Eye Syndrome

Women with 46,XX spontaneous POF have been shown to have an increased incidence of ocular surface disease as compared to control women (57). Findings meeting diagnostic criteria for dry eye syndrome were found in 20% of patients as compared with 3% of controls. The mechanism of the dry eye disease in these women has yet to be determined. For symptomatic women, referral for specialized evaluation and care is in order. There is controversy as to whether E therapy helps dry eye symptoms or makes them worse (58, 59).

Other Autoimmune Diseases

Although hypothyroidism and adrenal insufficiency are the most common autoimmune disorders to be found in association with spontaneous POF, the disorder may occur in association with other autoimmune diseases such as systemic lupus erythematosis (SLE) or myasthenia gravis (52). These are much less common, however, and laboratory evaluation for other autoimmune disorders should be directed by specific clinical indications.

Reproductive Health

Women with POF are relieved to learn that their chance of subsequent spontaneous conception is about 5%–10%, not zero (60). It is frustrating, however, that there are no proven therapies to improve ovarian function and increase this rate. The occult ovarian function that occurs is intermittent and unpredictable; therefore it is useless to attempt to time intercourse to improve conception rates. Those interested in conception should attempt to have coitus two or three times a week so sperm will be present should one of these unpredictable ovulations occur.

Hormone replacement therapy or use of OC as described will not prevent conception. To avoid prolonged fetal exposure to exogenous sex steroids, patients should keep a menstrual calendar and get a pregnancy test as soon as a menstrual period is late.

Once endocrine and emotional health issues relating to POF are satisfactorily addressed, couples are ready to move forward to make decisions about reproduction. Sufficient time needs to be given for grieving and emotional healing after couples receive the diagnosis of POF before making a decision about alternative family building options, such as donor egg IVF. Other options include childfree living for a while in the hopes of achieving a spontaneous pregnancy, choosing a life without children for the long term, adoption, or embryo donation. Unproven treatments should be avoided because they set patients up for failure. They also carry a real risk of interfering with a spontaneous conception that would have occurred had the system not been perturbed by the unproven intervention.

CONCLUSION

Young women who develop spontaneous POF have unique needs that require special care. The condition differs from normal menopause in several important ways. These patients benefit greatly from an integrated approach involving a solid and ongoing relationship with sensitive and well-informed clinicians.

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