What's the best approach to spontaneous premature ovarian failure?

By Lawrence M. Nelson, MD

Learning that she has what used to be called premature menopause can devastate a woman in her 20s or 30s. Diagnose this mysterious condition *without delay*, deliver the bad news in person, and provide sensitive answers to four basic questions.

Breaking the news to a 25-year-old woman that she has premature ovarian failure is no easy task, but you can soften the blow through compassionate counseling. Providing quality care to a young woman diagnosed with spontaneous premature ovarian failure (POF) is also challenging—and the extra time it demands of a busy ob/gyn can be frustrating. But it can also be extremely rewarding, especially when there's a multidisciplinary team in place to provide an integrated approach.

Spontaneous POF—the development of amenorrhea, sex hormone deficiency, and elevated serum gonadotropin levels before age 40—affects about 1% of women.[1] For the women with this disordered menstrual pattern whom we've seen at the National Institutes of Health (NIH) Clinical Center, the median age of onset is 25 years.[2] The term "spontaneous" means that the ovarian failure wasn't induced by chemotherapy, radiation therapy, or surgery. In the majority of cases the disturbance in menstrual regularity is a secondary development, as most of these patients have experienced normal puberty with menarche and the development of secondary sexual characteristics.[2,3]

The best approach to counseling a young woman with this disorder is to sensitively answer four key questions she'll bring to the office: (1) What is wrong? (2) Why did this happen? (3) What does this mean to my health? and (4) What should I do about this? My goal in this article is to do just that, beginning with the tests needed to diagnose it promptly. The key to caring for these patients is to view the problem primarily as a systemic disorder. The ovary is an endocrine organ as well as a reproductive organ. As such, ovarian failure induces hormonal deficiencies that have systemic effects, and ovarian failure may be linked with other endocrine deficiencies like hypothyroidism and adrenal insufficiency.

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What's wrong?

Patients often complain about how long it took them to get a diagnosis of POF. Certainly, the first clinical challenge is to diagnose this disorder early on (Table 1).

Take amenorrhea seriously. The most common presenting scenario is a young woman who develops secondary amenorrhea. Patients tell us that the initial laboratory evaluation often involved nothing more than a pregnancy test, and when that was negative no further evaluation was conducted. Through structured interviews, we have learned that more than one half of our patients who presented with secondary amenorrhea reported seeing three or more different clinicians before lab testing was performed to make the diagnosis.[2] The median time from the onset of a disturbed menstrual pattern to the time of diagnosis of premature ovarian failure was 2 years.

Do the right tests. Readily available commercial assays make it possible to quantify circulating steroid and protein hormone levels, enabling us to differentiate patients with amenorrhea into distinct etiologic categories. In 1990 Rebar and Connolly recommended laboratory evaluation for all women with amenorrhea to identify women with spontaneous POF or other types of amenorrhea.[3] Although a complete discussion about the differential diagnosis of secondary amenorrhea is beyond the scope of this review, a careful history and physical examination can lead to an appropriately targeted evaluation.[4]

Young women who've had irregular menstrual periods for 3 or more consecutive months deserve appropriate evaluation at their first office visit.[4] In general, at a minimum, this will include measurement of serum prolactin, FSH, LH, and estradiol (after pregnancy is ruled out). With the advent of modern laboratory methods there's no longer a need to substitute the progestin-withdrawal test for measuring serum FSH and estradiol levels. The withdrawal test may be misleading because many women with POF intermittently develop follicular-phase estradiol levels even in the face of markedly elevated FSH levels.[5] These patients will respond to the progestin challenge, which will delay the appropriate diagnosis.[3]

DR. NELSON is Chief, Gynecologic Endocrinology Unit, Section on Women's Health Research, Developmental Endocrinology Branch, National Institute of Child Health and Human Development. National Institutes of Health, Bethesda, Md.

Stephen E. Munz

Take-home messages

- Stress that there are no proven treatments to restore ovulation, but that premature ovarian failure (POF) can be transient, and that, in some cases, spontaneous remission can occur.
- Be prepared to sensitively answer the four key questions foremost on your patient's mind: (1) What is wrong? (2) Why did this happen? (3) What does this mean to my health? and (4) What should I do about this?
- When the "menstrual vital sign" is abnormal, seek out the cause as vigorously as you would for any abnormal vital signs such as pulse.
- Do a lab workup on all women with amenorrhea to promptly identify women with this disorder—and other types of amenorrhea.
- Be sure to identify the 4% of women who have ovarian failure caused by steroidogenic cell autoimmunity, because in some cases the POF may be the initial component of an autoimmune polyglandular failure syndrome.
- 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 you need to clarify this for patients.

Make the diagnosis. Women who have had 4 months without regular cycles and two FSH levels in the menopausal range (at least 1 month apart) meet diagnostic criteria for premature ovarian failure. The good news is that, in a community practice setting, fewer than 10% of women who present with secondary amenorrhea actually have spontaneous POF.[6] Nonetheless, these women deserve to be diagnosed early in the course of this condition to avoid the cumulative detrimental effects of estrogen deficiency on bone mass. Unfortunately, in roughly two thirds of the patients with spontaneous POF referred to our program, we detect osteopenia at their first visit.[7] I feel we should view the presence of regular menses in young women as *an important vital sign*, consistent with normal ovarian function. And when the "menstrual vital sign" is abnormal, physicians should seek out the cause as vigorously as we do for other abnormal vital signs, such as pulse.

Inform with sensitivity. Obviously, patients who wish to become pregnant find the diagnosis of POF particularly traumatic. For this reason, carefully plan your approach to delivering the bad news when informing patients. When you suspect this diagnosis, schedule a return visit to the office to review the laboratory results. (Some women have told me how emotionally traumatized they were when informed of the diagnosis over the telephone while at work.) Clinicians must anticipate the potential impact of something as seemingly insignificant as the terminology we use to describe the newly diagnosed condition on the patient's ability to handle the diagnosis in the most emotionally healthful way.

The term "spontaneous premature ovarian failure" is more accurate than "premature menopause" and more acceptable to patients. Menopause is defined as the permanent cessation of menses, which is not always the case with premature ovarian failure. Personally, I prefer the term "ovarian insufficiency" to describe this condition because from a physiologic standpoint it permits a continuum of insufficiency, and from an emotional perspective it provides some measure of hope.[8]

Why did this happen?

Spontaneous POF is a mysterious condition. In most cases that present as secondary amenorrhea no cause can be identified even after a thorough laboratory investigation. You'll need to discuss with a patient any genetic mechanisms of spontaneous POF that may have familial implications.[9] Two genetic evaluations to consider are the karyotype and *FMR1* premutation testing. In addition, it is critical to identify the 4% of women who have ovarian failure caused by steroidogenic cell autoimmunity, as in some cases the POF may be the initial component of an autoimmune polyglandular failure syndrome.[10]

Take a family history. It may be genetic, so it's critical to take a family history and document the

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pertinent positive and negative findings in the medical record. Refer women who have relatives with POF for genetic counseling. In rare cases familial POF can result from a structural abnormality in the X chromosome, and thus examination of a karyotype may be in order.[9] Also, familial POF can occur due to premutations in the *FMR1* gene, and specific testing for this condition is clinically available.[11] When fully mutated, the *FMR1* gene is the most common cause of familial mental retardation, and women who carry this premutation are at risk of having a child with fragile X syndrome. Also, the premutation state has been associated with a tremor/ataxia syndrome in older men, and less commonly in women.[12,13] In addition to women with a family history of POF, you should refer for genetic counseling women with POF who have a family history of unexplained mental retardation, developmental delay, dementia, or a tremor/ataxia syndrome. There are other rare genetic causes of familial premature ovarian failure (such as mutations in the FSH receptor[14]) for which routine genetic testing is not clinically indicated at the moment.

Unfortunately, there's currently no cost/benefit analysis available to determine what constitutes appropriate genetic evaluation for young women with POF who have no family history of the conditions just mentioned. Also, the ethical, legal, and social implications of such testing are still being debated. At this point the ideal solution might be to refer these patients to a research group that is funded to study the genetics of POF.

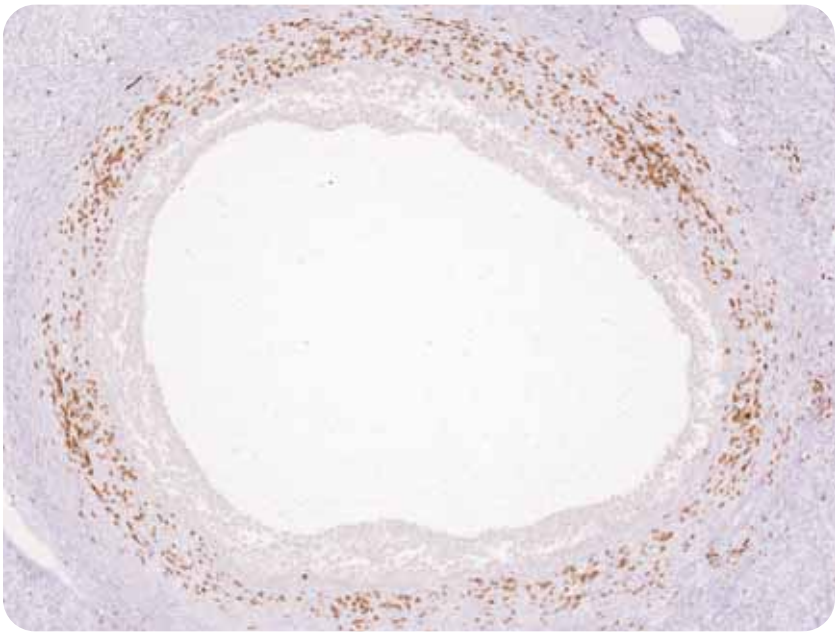

FIGURE 1. This micrograph depicts follicle dysfunction caused by autoimmune lymphocytic oophoritis in a young woman with spontaneous premature ovarian failure and positive adrenal antibodies. The brown stained cells are lymphocytes invading the theca of an antral follicle (original magnification 50×).

Our research laboratory is working specifically to define the mechanisms of 46,XX spontaneous POF. Thus, as part of our research protocol we routinely obtain a karyotype on all patients and count 50 cells to check for mosaicism. The purpose is to exclude X chromosomal abnormalities, which can cause spontaneous POF in women with no clinical evidence to suggest Turner syndrome.[9] Structural abnormalities of the X chromosome can have implications for other family members as well, but in the clinical setting the test is expensive and the yield would be low in the absence of a family history. In one report, an abnormal karyotype was found in 13% of women with spontaneous POF who presented with secondary amenorrhea at age 30 or younger, and in 56% of women who presented with primary amenorrhea.[2] In another report, one of 40 women with spontaneous POF presenting as secondary amenorrhea had an abnormal karyotype.[15]

Testing for premutations in the *FMR1* gene in women with spontaneous POF and a negative family history raises complex issues. Approximately 6% of women who present with spontaneous POF have premutations in the *FMR1* gene, and the risk is higher if there is a family history of the disorder.[11] Curiously, however, not all women with the *FMR1* premutation—merely 16%—develop POF.[16] Clearly there is a need for more research.

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Measure adrenal antibodies. That will tell you if the patient is at risk for autoimmune adrenal insufficiency and autoimmune lymphocytic oophoritis (Figure 1), the mechanism of ovarian failure in steroidogenic cell autoimmunity, which was originally linked with Addison disease.[17,18] A striking characteristic of autoimmune oophoritis is the way primordial follicles are spared, despite the presence of intense lymphocytic infiltration in the theca of developing follicles.[19] That sparing opens up the theoretical possibility of developing treatments that could restore fertility. Our group is currently conducting a randomized controlled study evaluating alternate day prednisone therapy as a treatment for autoimmune oophoritis (http://pof.nichd.nih.gov). There is no need to test for ovarian antibodies, which are known to be unreliable and have a high false-positive rate.[20,21]

Autoimmune oophoritis is associated with steroidogenic cell autoimmunity, which is evident in about 4% of women who present with spontaneous POF as their primary concern. Testing for serum adrenal autoantibodies using a commercially available indirect immunofluorescence assay will identify these women.[22] The test is critical because autoimmune adrenal insufficiency (Addison disease), is a potentially fatal condition. Women with positive adrenal antibodies will require referral to a medical endocrinologist for additional evaluation and long-term follow-up of their adrenal function.

What does this mean to my health?

Young women are rightly concerned about the effects of spontaneous POF on their general health. Advise these patients that the diagnosis has major implications for their endocrine, emotional, and reproductive health. A woman with POF once told me that on hearing this diagnosis "the only thing I could think about was how to get a baby." A newly diagnosed young woman's own endocrine and emotional health should be her first priority, so be sure to emphasize that point. Only after adequately addressing these issues is it time to make reproductive health decisions.

Endocrine health. Because women with POF are deficient in ovarian sex hormones, they may have vasomotor symptoms, sleep disturbance, and vaginal dryness and be at increased risk for developing osteoporosis and cardiovascular disease.[7,23,24] They also have a higher risk for developing autoimmune thyroid disease.[25] As mentioned earlier, women who have a positive adrenal antibody test are at risk for adrenal insufficiency and should be managed accordingly.[22] Although as a group, women with POF are testosterone deficient, the clinical significance of this is not clear.[26] It's recently come to light that young women with this disorder have an increased incidence of dry eye syndrome, the mechanism of which is unclear.[27] Refer women with symptoms of dry eye for evaluation and appropriate management.

Emotional health. Because POF can cause psychological distress, some researchers have suggested including psychological care in its management.[28] Understandably, these young women are emotionally unprepared for such a diagnosis. Some women describe hearing the news of the diagnosis as similar to learning about a death in the family. Feelings of loss and grief, combined with the disturbed sleep and other physical symptoms of estrogen deficiency create a very special and, perhaps, unique set of needs.

Reproductive health. It's also understandable that women who wish to have children might feel an urgent need to act immediately to achieve a pregnancy when diagnosed with POF. It is important to stress two points: (1) There are no proven treatments that will restore ovulation, and (2) POF can be transient, and—in some cases—spontaneous remission can occur.[3]

At one time, the pathophysiology of spontaneous POF was thought to be no more than just an early menopause. Normal menopause occurs because the ovaries exhaust their store of primordial follicles; in other words, women experience normal menopause because of "follicular depletion." In contrast, roughly 50% of women with spontaneous POF have "follicular dysfunction," in which some primordial follicles still remain in the ovary,

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but something prevents them from working normally.[29] There is currently no proven treatment to predictably restore these follicles' ability to function and, in turn, restore fertility. Even so, the remaining follicles may function intermittently and unpredictably, produce estradiol, and sometimes even ovulate.

The good news is that roughly 10% of patients diagnosed with this disorder will later become pregnant at some point. The clinical situation is not hopeless; rarely can a clinician categorically rule out the chance of a subsequent spontaneous pregnancy. In fact, pregnancy can occur even many years after the diagnosis.

TABLE 1

What's the best approach to spontaneous premature ovarian failure?

Make the diagnosis promptly.

Inform the patient of the diagnosis in a sensitive and supportive manner.

Counsel the patient in a way that validates her emotional concerns.

Take a detailed and specifically directed family history.

Consider the need for a karyotype and *FMR1* testing.

Refer for genetic counseling as indicated.

Test for adrenal autoantibodies and refer for evaluation of adrenal function in those who are positive.

Inquire about dry eye symptoms and refer appropriately.

Measure TSH, free T4, and thyroid peroxidase autoantibodies.

Provide cyclic estrogen and progestin replacement to induce monthly withdrawal bleeding.

Have the patient keep a menstrual calendar and obtain a pregnancy test promptly if her menses is late.

Educate about the need for adequate calcium intake, weight-bearing exercise, and vitamin D to maintain bone health.

Delay decisions regarding reproduction until endocrine and emotional health issues are managed appropriately.

What should I do about this?

Empower patients by encouraging them to become active participants in their health care. Tailor solutions to each individual.

Endocrine health. Many women with spontaneous POF have significant fears about estrogen therapy. It is not scientifically valid to apply results of the Women's Health Initiative, a study of menopausal women, when making decisions about hormonal therapy in young women with POF. Clinical judgment suggests that remaining sex-hormone deficient as a young woman carries a greater health risk than does replacing the hormones normally supplied by the ovaries. In this sense, hormonal therapy is truly replacing ovarian hormones, just as treatment for juvenile diabetes replaces insulin. At age 50, women who have experienced POF then join the ranks of normally menopausal women and can be managed as such. In a nutshell, 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 you need to clarify this for patients.

There's certainly room for individual recommendations, but in my clinical judgment, I recommend that patients first try the 100-µg estradiol transdermal patch, which averts the first-pass effect on the liver. My first-line progestin replacement is medroxyprogesterone acetate, 10 mg/day, for 12 days each month. More research is needed regarding the need for androgen replacement. Because these women are at increased risk for osteoporosis, advise them about calcium intake (1,200 to 1,500 mg/day), daily weight-bearing exercise, and the need to take a daily multivitamin to avoid vitamin D deficiency. Thyroid and adrenal hormone replacement should be managed as indicated.

Emotional health. It's important to refer women to accurate sources of information about spontaneous POF. You can also help them by giving them permission to express their emotions about the diagnosis, and then val-

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idate those feelings by reassuring them that their feelings are normal and expected. A simple statement such as "many patients with premature ovarian failure feel that this is a very difficult diagnosis to accept emotionally" can be an effective entrée into this discussion. It helps to briefly explain the normal grieving process. Most women with POF will benefit from referral to a professional counselor for a baseline evaluation, and in some cases ongoing individual or group counseling might be recommended. Encourage women with POF to participate in a support group, which can help reduce feelings of isolation and loneliness. One outstanding resource is the POF Support Group (www.pofsupport.org), founded by Catherine Corp, RN, MPH.

Reproductive health. Most women with POF are relieved to learn that their chance of subsequent spontaneous conception is about 10%, which at least is not zero. However, they're frustrated by the lack of proven therapies to improve this rate. Ovarian function is intermittent and unpredictable in POF, so it is useless to attempt to time coitus to improve conception rates. Tell women who want to become pregnant to attempt intercourse two or three times a week, so that sperm will be present in the event that one of these unpredictable ovulations takes place. Hormone replacement therapy as I've described will not prevent conception, and patients should keep a menstrual calendar and get a pregnancy test as soon as their menstrual period is late to avoid prolonged fetal exposure.

For women who want to *avoid* pregnancy, a barrier method is advised because hormonal contraception is not reliable in these women due to the elevated gonadotropin levels. Once couples have satisfactorily addressed endocrine health and emotional health, they can move forward to make decisions about reproduction. Plans could include child-free living for a while in the hopes of achieving a spontaneous pregnancy, child-free living for the long term, adoption, egg donation, or embryo donation. Advise against unproven treatments that set patients up for failure and carry real risk of interfering with a spontaneous conception that would have occurred had the system not been perturbed by the unproven intervention.

Patients' special counseling needs

Because young women who develop spontaneous POF have special needs, they require special care. The condition differs from normal menopause in important ways. The time constraints currently imposed on clinicians can make caring for a woman with POF a frustrating experience, both for patient and clinician. Our research program has the added responsibility of obtaining informed consent, which allots us adequate time to see these patients. We meet with each patient and her partner for a 3-hour session to explain normal ovarian physiology and to address the issues I've discussed. We also have the advantage of a multidisciplinary team to help meet the needs of these women. These patients benefit greatly from a solid and ongoing relationship with a sensitive and well-informed health-care practitioner. Those clinicians who meet the special needs of these patients will find the experience both satisfying and rewarding. ☐

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