Spontaneous Premature Ovarian Failure: Young Women, Special Needs

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The diagnosis of spontaneous premature ovarian failure can be a difficult one for young women, especially those desiring fertility. These women fare best when their clinicians understand and are prepared to meet the special needs that arise from this diagnosis.

Introduction

Spontaneous premature ovarian failure causes cessation of regular menstrual periods, development of infertility and symptoms of the menopause in young women (before age 40). Half of the women with premature ovarian failure seen at the NIH Intramural Research Program develop the condition before the age of 32, and we have seen it in girls as young as 14.

As defined by the World Health Organization, ovarian insufficiency can be the result of a primary disorder in the ovary or of secondary causes, such as anorexia nervosa.[1] Ovarian insufficiency is considered primary if the ovary fails to function normally in response to appropriate gonadotropin stimulation via the hypothalamus and pituitary; it is considered secondary if the hypothalamus and pituitary fail to provide appropriate gonadotropin stimulation as, for example, in the presence of a pituitary prolactinoma. Primary ovarian insufficiency in its fully developed form is known as premature ovarian failure, the criteria for which are at least 4 consecutive months of amenorrhea and two serum FSH levels >40 mU/mL (drawn at least a month apart).[2]

There was a time when the pathophysiology of spontaneous premature ovarian failure was thought to be no more than just an early onset of the natural menopausal process; the condition was even referred to as "premature menopause." We now know that spontaneous premature ovarian failure is not simply an early menopause.[3] The normal menopause occurs because the ovaries exhaust their store of critical primordial follicles; in other words, women experience normal menopause because of "follicle depletion." The situation is not the same for many women with spontaneous premature ovarian failure. Approximately 50% of these women have what is termed "follicle dysfunction," in which there are still primordial follicles remaining in the ovary, but something prevents them from working normally. There is currently no proven treatment to predictably restore these follicles' ability to function and, in turn, restore fertility.[2] Nonetheless, the remaining follicles can still function to a degree by producing estradiol and, sometimes, ovulating intermittently and unpredictably; at times, a spontaneous pregnancy can occur many years after the diagnosis.[4]

Special Considerations

Although the symptoms can be similar, spontaneous premature ovarian failure differs from the normal menopause process in many important ways, and the needs of young women with the condition differ significantly from those of normally menopausal women.

It is understandable that these young women are emotionally unprepared for such a diagnosis, since even women who experience natural menopause in their 50s often grapple with emotional issues related to the end of fertility, and to body image, sexuality, aging and the long-term health implications of the associated estrogen deficiency. This is true even though menopause is an expected physiologic event in midlife, and a period of preparation and adjustment is normally afforded by the preceding perimenopausal transition. Women who experience spontaneous premature ovarian failure are not afforded the "luxury" of such an adjustment period.

Often, young women tell me that when they were first informed of the diagnosis of premature ovarian failure, they felt as if there had been a death in the family and that a part of their lives had been taken away. These women often feel as if they have become strangers in their own worlds; they describe feelings of isolation and loneliness, especially as their peers continue to plan and create their families or discuss the need for contraception. To complicate matters further, the cause of the ovarian failure remains a mystery in most cases, even after a complete medical evaluation. It is well known that grieving over a loss is much more difficult when the cause of that loss remains elusive. These 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. The patient with spontaneous premature ovarian failure will fare best when her clinician is prepared to meet and respond to her special needs with care and understanding.

Our research group began studying spontaneous premature ovarian failure on the campus of the National Institutes of Health in 1988. Since then we have seen more than 250 women with the condition. Over the years our patients have told us how they would prefer to have their needs met. Based on that information—and our own clinical judgment—we recommend that clinicians caring for such patients do the following:

- Make the diagnosis promptly and accurately;
- Inform the patient of the diagnosis in a sensitive and supportive manner;
- Counsel the patient in a way that validates her emotional concerns and helps her to maintain control of her physical and emotional health;
- Provide cyclic estrogen and progestin replacement; and
- Assess and continue to reassess for the presence of other disorders related to spontaneous premature ovarian failure.

Making the Diagnosis

Young women who begin to skip menses should seek medical evaluation; in some cases skipped menstrual periods can be the earliest sign of impending ovarian failure and can be detected with serum follicle-stimulating hormone (FSH) measurement. Patients often complain to me that the diagnosis of premature ovarian failure seemed to be delayed inappropriately. The most common scenario these women describe is one in which the clinician ascribes loss of menstrual regularity to stress (something we all experience), without suggesting or initiating appropriate evaluation.

Young women who experience loss of menstrual regularity for 3 or more con-

secutive months deserve appropriate evaluation at their first visit to a clinician. In young women the presence of a regular menses can be viewed as an important vital sign, consistent with good health. When the "menstrual vital sign" is abnormal, the etiology should be sought out with the same vigor as is applied to other abnormal vital signs, such as pulse.

Women with early stages of premature ovarian failure can present with any of several types of menstrual disorders, including metrorrhagia, polymenorrhea, oligomenorrhea and amenorrhea. Metrorrhagia is more commonly associated with cervical or endometrial pathology but, in some cases, can be an early sign of ovarian insufficiency. If careful history and physical examination, cervical cytology, and cultures for gonorrhea and chlamydia fail to explain the symptom, serum FSH and estradiol measurments might reveal developing ovarian insufficiency. Likewise, the development of polymenorrhea (menstrual cycles less than 21 days in length) can also be an early sign of developing ovarian insufficiency. In women who desire fertility, polymenorrhea is an indication for FSH and estradiol measurement on day 3 of the cycle.

A careful history and physical examination can narrow the differential diagnosis of secondary oligomenorrhea or amenorrhea. Women with evidence of androgen excess, or with signs and symptoms of systemic disease (e.g., hyperthyroidism or adrenal insufficiency), eating disorders, cocaine/narcotic abuse (or therapeutic use of psychotropic drugs), galactorrhea or a history to suggest outflow tract abnormalities will require specific, appropriately targeted evaluation. For the remaining women with oligomenorrhea or amenorrhea, we recommend obtaining levels for serum prolactin, FSH and estradiol (after pregnancy has been ruled out). We advise against the use of progestin-withdrawal testing as a substitute for serum FSH and estradiol measurement, since some women with premature ovarian failure develop follicular-phase estradiol levels in the face of markedly elevated FSH levels; these women respond to the progestin challenge and the appropriate diagnosis is delayed.[2] Women who have 4 months of amenorrhea and two FSH levels >40 mU/mL (at least 1 month apart) meet our diagnostic criteria for premature ovarian failure. For these women we recommend obtaining a karyotype. Fewer than 10% of women who present with disordered menses will ultimately be found to have spontaneous premature ovarian failure. Nonetheless, these women deserve to have their condition diagnosed early in its course to avoid the cumulative detrimental effects of estrogen deficiency on bone mass. Approximately two-thirds of the patients with spontaneous premature ovarian failure seen in our practice have osteopenia at the first visit.[5] We recently surveyed a group of our patients to investigate the possibility that delay in diagnosis might play a role in the development of osteopenia in such women, and found that the duration between the onset of loss of menstrual regularity and the time of diagnosis had often been longer than 1 year. In addition, many patients had seen three or more physicians before the diagnosis of premature ovarian failure had finally been established.

It is important to remember that the ovary functions both as an endocrine organ and a reproductive organ. Young women often tell me that no laboratory evaluation of their abnormal menstrual pattern was undertaken at their first office visit because they were not interested in fertility at the time. As an endocrine organ, the ovary maintains health in young women by secreting steroid hormones such as estrogens, androgens and progesterone. An abnormal menstrual vital sign might herald deficient ovarian endocrine function. Ovarian endocrine insufficiency, whatever the etiology, is associated with bone loss.[6]

Informing the Patient

Patients who desire fertility find the diagnosis of premature ovarian failure particularly traumatic. For this reason a carefully planned approach is required when informing patients of this diagnosis. It is best to schedule a return office visit to review the laboratory results when the diagnosis is suspected. (Some patients have told me about the emotional trauma they experienced as a result of being informed of the diagnosis by telephone while they were at work.)

It is important to stress to patients that even premature ovarian failure (primary ovarian insufficiency) can be transient and that, in some cases, spontaneous remission can occur. Pregnancy will occur spontaneously subsequent to the diagnosis in approximately 10% of patients. The clinical situation is not hopeless; rarely can a clinician categorically rule out the chance of a subsequent spontaneous pregnancy. Pregnancy has even occurred at age 44 in a patient diagnosed with premature ovarian failure at age 28.[7]

It is also important to understand that something as seemingly insignificant as the terminology used to describe the newly diagnosed condition can have an impact on the patient's emotional ability to handle the diagnosis in the most healthful way possible. The term "premature menopause" seems to carry excess baggage for young women; "premature ovarian failure" is more accurate and more acceptable to both clinicians[2] and patients. My personal preference, and one that tends to be shared by my patients, is the term "primary premature ovarian insufficiency" (currently used in the French medical literature).[8] This term is more accurate still; from a physiologic standpoint it permits a continuum of insufficiency, and from an emotional perspective it provides some measure of hope.

Counseling and Validating

The young woman with premature ovarian failure brings many concerns to her clinician's office. It is important that the clinician validate the patient's appropriate concerns and, by the same token, educate

the patient to help allay any concerns that might be ill-founded.

Fertility. It is understandable that patients who desire fertility might feel an urgent need to act immediately to achieve a pregnancy when diagnosed with premature ovarian failure. It is important to stress that there are no prospectively proven treatments that will restore ovulation, and couples should be informed of the risks and benefits of all options. Gonadotropin therapy carries a theoretic risk of exacerbating unrecognized autoimmune ovarian failure.[9] Prednisone therapy for suspected autoimmune ovarian failure is unproven and carries a risk of osteonecrosis of the hip and the need for joint replacement.[10] Also, although rarely considered, unproven therapies carry a real risk of interfering with a spontaneous conception that would have occurred had the system not been perturbed by the unproven intervention.

Many couples decide to avoid the intrusion of high technology into their private lives and choose adoption or a change in their life goals to resolve their problem with infertility. Some couples are satisfied to accept the small, but real, chance that their infertility will resolve spontaneously over the years. Ovum donation is a successful solution for some couples. Although the patient and her partner might feel a sense of urgency about proceeding with ovum donation, there is, in reality, no rush. The success of ovum donation depends primarily on the age of the ovum donor;[11] thus, ovum donation as a solution for the infertility associated with premature ovarian failure is as successful in older women as it is in younger women. It is wise for couples to delay proceeding with ovum donation until they feel they have dealt sufficiently with emotional issues, such as those described below.

Solutions should always be tailored to the individual. Many couples, for example, prefer to avoid egg donation for several reasons. Alternative resolutions, such as a change in life plans, adoption or simply allowing more time for the possibility of spontaneous conception which, as mentioned previously, occurs in 10% of these women, are more appropriate solutions for some couples. Couples should be advised to avoid unproven fertility therapies that will likely set them up for failure.

Grief and loss. For those patients whose life plans included building a family, intense feelings of grief and loss for the biologic children they expected to have are normal and expected. Validating those feelings and assuring the patient that it is normal to grieve over this (in a sense, giving her permission to grieve) is therapeutic.

A brief explanation of the normal grieving process can be helpful. Such an explanation will validate that the normal grieving process for any significant loss usually includes stages of denial, anger, loneliness, isolation, depression, self-doubt, self-blame, guilt, jealously and resentment.[12] Asking the patient how she feels about the diagnosis and permitting her to ventilate in the office is therapeutic; it validates her trust in her clinician, as someone who takes her situation seriously. It is important to include the spouse in this process and to stress the need for clear communication regarding strains that the diagnosis might bring to the relationship.

Effects on health. Young women with premature ovarian failure are appropriately concerned about effects on their general health. Many of these women are aware that estrogen deficiency in menopausal women has been associated with osteoporosis and an increased risk of cardiovascular disease. It is important to validate these concerns, but also to point out that it is possible to avoid these ill-effects by maintaining a healthy lifestyle (avoiding smoking, getting adequate exercise, eating a healthy diet and ensuring adequate calcium intake) and taking hormone replacement therapy.

Many women with premature ovarian failure have significant fears that estrogen replacement will increase their cancer risk; they mistakenly, and inappropriately, apply the media-espoused risk/benefit analysis for menopausal women to their own situation. It is important to stress to patients that women with premature ovarian failure differ from normally menopausal women. In women with premature ovarian failure, the objective is to replace the hormones that the ovary would normally be producing until age 50. In this sense, hormonal therapy is truly *replacing* ovarian hormones, just as prescribed treatment for individuals with juvenile diabetes replaces insulin.

In young women, the ovaries normally provide endogenous sex steroid hormones which, in turn, help to maintain good health. 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. At age 50, women who have experienced premature ovarian failure can decide if they wish to *extend* hormone replacement therapy (HRT), as is decided by some normally menopausal women. 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 premature ovarian failure, and this needs to be clarified for patients.

Dealing with emotions. As with any life-altering diagnosis, the diagnosis of premature ovarian failure can induce a sense of loss of control and helplessness. It is important for the clinician to help patients regain a sense of control and confidence. The first step along this path involves encouraging the patient, when she is ready, to express the emotions she is feeling about the diagnosis; these women need emotional encouragement and support.

Women with spontaneous premature ovarian failure often need a trusted healthcare practitioner to, in essence, give them permission to feel their emotions about the diagnosis, and then validate those feelings. Among the clinician's major goals are to gently and indirectly encourage patients to express their emo-

tions, permit them to fully experience these emotions, and help them to understand 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 is also important for patients to discuss their feelings about the diagnosis with their partners, family members, trusted close friends or clergy. The clinician should point out that coming to grips with emotions about this diagnosis is a gradual process; the patient needs to give herself time, and permission, to work through these issues.

Encouraging women with premature ovarian failure to contact a support group can be extremely helpful, as participating in such a group is an effective way for these women to reduce the feelings of isolation and loneliness that many of them experience. Ideally, the support group should be one specifically for young women who have premature ovarian failure. (Young women have told me that attending meetings of groups for older, normally menopausal women has actually *increased* their feelings of isolation and loneliness.) One outstanding support group for young women with premature ovarian failure is the POF Support Group **(www.pofsupport.org)**, founded by Catherine Corp, RN, MPH. If there is no such support group near a patient's home or workplace, this group can assist the patient in getting one started. Starting a local support group is a powerful way for patients to regain a sense of control and confidence.

There are several other avenues by which clinicians can help women with premature ovarian failure to regain control, including steering them to accurate sources of information about the diagnosis and encouraging them to become better informed. Some young women misinterpret the diagnosis of premature ovarian failure as an indication that they have become a menopausal woman who is "growing old overnight." Vasomotor symptoms and vaginal dryness can be interpreted as signs of aging, rather than signs of estrogen deficiency. It is important to make a point of explaining that this is not the case, and to again stress the ways in which premature ovarian failure differs from the normal menopause. To this end, the clinician should make certain that the patient and her partner understand the following points.

Menopause and aging are related, but are independent of one another. Menopause is defined as the permanent cessation of menses and occurs, on average, at about age 50. When a woman experiences menopause, fertility and the maintenance of follicular estrogen levels have definitively ended. When a woman experiences premature ovarian failure—or premature ovarian insufficiency—there is often intermittent and unpredictable ovarian function for decades and, sometimes, even a spontaneous pregnancy many years after the diagnosis.

Patients should be encouraged to become active participants in their health care by providing them with choices related to addressing the issues they face. Empowerment through choice can apply to a range of areas, such as the types of exercise patients can do to help maintain bone density, the types of foods that will maintain calcium intake and the type of hormone replacement they will take. As stated above, solutions should be tailored to the individual patient.

Our group has been impressed with the amount of underlying anxiety and depression we see in our patients with spontaneous premature ovarian failure; we are currently collecting data in this area. There was a time when we recommended referral to a mental health professional for counseling only when the need was overt. We now recommend to all patients with spontaneous premature ovarian failure that they consider undertaking a three-session visit with a professional counselor for a baseline evaluation. We made this change after realizing how much subclinical depression and anxiety this group of patients brings to the clinic. In some cases, ongoing individual or group counseling might be recommended.

Providing Hormone Replacement

Young women with premature ovarian failure need full-dose estrogen replacement, rather than the lower doses of estrogen that are used for osteoporosis prophylaxis in normally menopausal women; low-dose estrogen does not maintain bone density as effectively in younger women. In addition, young women with premature ovarian failure should be given cyclic estrogen and progestin replacement therapy that will induce regular menses. This is important because of the potential for spontaneous and unexpected pregnancy. If the patient misses a period on this regimen, a pregnancy test should be performed and the hormone replacement stopped. In our clinical experience these spontaneous pregnancies progress normally in most cases, and there appears to be no need for exogenous hormone supplementation during early pregnancy.

Many HRT regimens are available for these women; there certainly is room for individual recommendations. Based on our clinical judgment we recommend that patients with premature ovarian failure first try the 100-mg estradiol transdermal patch, which averts the first-pass effect on the liver by delivering the estradiol parenterally in a constant infusion. For women who do not tolerate the patch, oral estrogen therapy is a good alternative. Our first-line progestin replacement is medroxyprogesterone acetate (MPA) 10 mg/day for 12 days each month. Other progestin regimens, such as oral micronized progesterone, can be good alternatives for some women who prefer not to take MPA. More research is needed regarding the need for androgen replacement. Participants are currently being sought for an NIH study of transdermal estradiol plus testosterone for premature ovarian failure (see "News Briefs," p. 36.)

Assessing and Reassessing

Women with spontaneous premature ovarian failure are at risk for developing other endocrine gland failure conditions. In some cases the ovarian failure can be a component of an autoimmune polyglandular failure syndrome.[14] At the National Institutes of Health we prospectively evaluated 119 patients with karyotypically normal spontaneous premature ovarian failure and found that 32 (27%) had hypothyroidism and three (2.5%) had adrenal insufficiency.[15] We recommend laboratory screening for hypothyroidism and adrenal insufficiency when the diagnosis of spontaneous premature ovarian failure is first established. In our practice we screen for hypothyroidism by measuring serum free thyroxine and thyroid-stimulating hormone levels, and for autoimmune adrenal insufficiency by measuring adrenal antibodies.[16] Patients might require referral for the evaluation and treatment of these conditions.

We recommend that, in general, patients with spontaneous premature ovarian failure be seen annually for evaluation of their HRT regimens. Vigilance is in order to identify the few patients who will subsequently develop other components of a polyglandular failure syndrome or non-organ-specific autoimmunity. Patients should be forewarned regarding the early symptoms of adrenal insufficiency, a potentially fatal disorder that is readily treated once identified.

Summary and Conclusions

Young women who develop spontaneous premature ovarian failure have special needs and, therefore, require special care. Because this condition differs from the normal menopause in several important ways, the needs of the patients differ, as well. Clinicians need to validate patients' appropriate concerns in a sensitive manner, while helping to allay ill-founded concerns. It is important to help patients regain a sense of control and confidence by appropriately addressing the emotional issues and physical health concerns that accompany the diagnosis of spontaneous premature ovarian failure. Encouraging patients to contact a support group specifically designed for women with the same condition will provide them with an effective way to help reduce the feelings of isolation and loneliness that many of these women experience.

Young women with premature ovarian failure need full-dose estrogen replacement regimens, rather than the lower estrogen doses that are often used for osteoporosis prophylaxis in women who experience normally occurring menopause. Vigilance is in order to identify the few patients who will subsequently develop other components of polyglandular failure syndrome or non-organ-specific autoimmunity.

Finally, patients with spontaneous premature ovarian failure benefit greatly from a solid and ongoing relationship with a sensitive and well-informed healthcare practitioner. The time constraints currently imposed on clinicians can make caring for a woman with premature ovarian failure a frustrating experience, both for patient and clinician. As clinicians in a research facility, we have the added responsibility of obtaining informed consent and are thus allotted adequate time to see these patients. We meet with each patient and her partner for a 2-hour session to explain normal ovarian physiology and to address the issues discussed above. We also have the advantage of a multidisciplinary team to help meet the needs of these patients. Those clinicians who have the resources available to meet the special needs of these patients will find the experience both satisfying and rewarding. ■

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Reprinted from *Menopause Management* magazine • July/August 2001 • Volume 10, Number 4
A Medquest Communications LLC publication • 3800 Lakeside Ave., E., Cleveland, OH 44114 • PH 216-391-9100 • FAX 216-391-9200