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A New Approach to Primary Ovarian Insufficiency

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INTRODUCTION

Recently the National Institutes of Health convened a stakeholders meeting on primary ovarian insufficiency to explore ways in which to advance the field. The published report stressed the need for an integrative approach.¹ Women with primary ovarian insufficiency face the acute shock of the diagnosis; associated stigma of infertility; grief from the death of dreams; anxiety and depression from the disruption of life plans; confusion around the cause; symptoms of estrogen deficiency; worry over the associated potential medical sequelae, such as reduced bone density and cardiovascular risk; and the uncertain future that all of these factors create.^{2,3} Evidence supports a role for a collaborative care model as a method to improve medical outcomes, reduce costs, and to do so in a way that clinicians find satisfying.^{4–6} This approach should be combined with the development of a public health knowledge network on primary ovarian insufficiency.^{7,8} This knowledge network would form the central component of a community of practice for the condition.^{9,10}

The authors' research team now includes a reproductive endocrinologist, reproductive psychiatrist, medical endocrinologist, occupational therapist, recreational therapist, nutritionist, chaplain, and social worker. They have learned that they need to know the patient at a personal level to care for them appropriately. Before evaluation, all of their patients answer a series of questions in writing about themselves and how primary ovarian insufficiency has affected their lives (Box 1). The authors call this "The Patient Narrative" and share it in confidence with the entire team. This practice has changed their team dynamics and given greater meaning to their work.

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Box 1**Patient narrative questions for women with primary ovarian insufficiency to answer in writing**

- a. What would you like us to know about you as a person?
- b. How would you like your life to change in the next six months?
- c. What are your aspirations for your life in the long term?
- d. What gives your life meaning and purpose?
- e. If nothing changed in your life right now what would that mean to you?
- f. What were your dreams about your future family life before you found out that you have primary ovarian insufficiency?
- g. How has primary ovarian insufficiency affected your life?
- h. Please give us an example of a difficult situation in your life from the past (other than your diagnosis of primary ovarian insufficiency) and explain to us how you coped with that.
- i. How do you cope with the diagnosis of primary ovarian insufficiency?
- j. What fears do you have about the diagnosis of primary ovarian insufficiency and how it will affect your future?
- k. What fears do you have about your visit here?
- l. Is there anything else that you want us to know about you?

For most women the infertility associated with the diagnosis is the most upsetting component of the disorder (Box 2).¹¹ However, primary ovarian insufficiency involves many aspects of a woman's life. It is a serious chronic disease that requires long-term management. Chronic illnesses change people's lives. Patients and their caregivers are abruptly confronted with a restricted and uncertain future. They also acquire new burdens associated with managing the disease.^{6,12} In most cases couples discover they are infertile in a gradual manner after many failed attempts at conception. In stark contrast, for most women with primary ovarian insufficiency knowledge of the diagnosis arrives abruptly and unexpectedly as part of an evaluation for oligo/amenorrhea or polymenorrhea, in many cases even before they have a partner or have even attempted conception.¹³

Box 2**Worries articulated by a patient advocate with primary ovarian insufficiency**

- What if my pregnancy test never turns positive?
- What if I never fill my baby scrapbook page?
- What if my infertility robs me of my sexiness and I'm never "in the mood again"?
- What if we finally save enough money for our one egg donation cycle and it fails?
- What if we can't afford to adopt?

- What if I can't counter the thought that I had to "buy" a baby?
- What if I have to read another pregnancy announcement in an online social media today?
- What if we have to learn to live child free... with a smile?
- What if he leaves me for a fertile woman?
- What if I never let go of the resentment and jealousy of the woman who got to do this naturally?
- What if I lose myself along the way?
- What if I stop defining myself by my infertility?
- What if I stop hiding behind my fears?
- What if I stop hiding behind my grief?
- What if I redefine what it means to be a woman?
- What if I redefine what it means to be a mother?
- What if I redefine what it means to be a family?
- What if I let go of the doubt, the fear, the worry, and the self-judgment for one day?
- What if I lived in the moment rather than in an uncertain future?

Courtesy of Keiko Zoll, writer and founder of TheInfertilityVoice.com; with permission.

"Devastated," "shocked," and "confused" are the most common words women use to describe their feelings in the hours after being informed of this diagnosis.¹⁴ These are words that describe emotional trauma. Many clinicians resolve during their early years of training to learn from their patients, listen attentively to them, and to provide culturally appropriate, patient-centered care. Then the tyranny of reality takes over.¹⁵ The past few decades have brought incredible progress to the scientific underpinnings of reproductive medicine. Some of these technologies have taken precedence over a critical skill of the compassionate clinician: the art of listening to the patient.¹⁶ A recent report that compared physician career satisfaction with their chosen specialty showed that obstetrics and gynecology scored unfavorably.¹⁷ Similarly, most women with primary ovarian insufficiency get their diagnosis from a gynecologist, and most of them are unsatisfied with how they were informed about it.¹⁴ A focus on problem-solving often blinds physicians to emotional issues in their patients and themselves.¹⁸ It seems that both sides of the equation in this dilemma see room for improvement in the shared experience of primary ovarian insufficiency.¹⁹

OVARIAN PHYSIOLOGY

Estradiol is by far the most potent of the three major natural human estrogens: estradiol, estrone, and estriol. The dominant graafian follicle, which develops anew each month within the ovary, is the main source of estradiol in reproductive-aged women. The graafian follicle develops from microscopic primordial follicles, the structures in the ovary where oocytes are stored. The primordial follicle number peaks at 6 to 7 million by 20 weeks of gestation in a human female fetus.²⁰ Thereafter they rapidly undergo atresia leaving only 1 to 2 million oocytes at birth. At puberty there are only 300,000 of the original 6 to 7 million left, of these only 400 to 500 oocytes are released during ovulation in the entire reproductive life.²¹ Menopause, the permanent cessation of menses, occurs because of depletion of functional

primordial follicles. The mean age of menopause is 50 ± 4 years and if it occurs before 40 years it is considered premature.²²

THE CLINICAL PROBLEM

Primary ovarian insufficiency is the preferred term for this condition.^{2,23,24} The term was initially used in 1942 by Fuller Albright, who first described the condition and who many consider to be the father of modern endocrinology. His research report made it clear that the amenorrhea was caused by impaired ovarian function as the primary cause rather than a pituitary disorder (secondary cause).^{23,25} Other terms, such as premature ovarian failure, premature menopause, early menopause, hypergonadotropic hypogonadism, ovarian dysgenesis, and hypergonadotropic amenorrhea, have also been used in the literature to describe the condition.¹

Presentation

Primary ovarian insufficiency affects 1 in 10,000 women by age 20, 1 in 1000 by age 30, and 1 in 100 by age 40.²⁶ Although primary amenorrhea may be the initial symptom in 10% of cases, more often patients present with irregular menstrual cycles in the form of oligo/amenorrhea, polymenorrhea, or dysfunctional uterine bleeding after having attained normal puberty and having established regular menstrual cycles.²⁷

Diagnostic Criteria

To meet diagnostic criteria for primary ovarian insufficiency patients need to be younger than 40 years of age, have experienced 4 months of oligo/amenorrhea, and on investigation be found to have two serum follicle-stimulating hormone (FSH) levels in the menopausal range, obtained at least a month apart (Box 3).²⁷⁻²⁹ Evidence has demonstrated that most women with primary ovarian insufficiency experience intermittent ovarian function rather than complete cessation of ovarian function. Therefore, most of these patients are expected to have irregular and unpredictable menses rather than complete amenorrhea. Hence, a period of complete amenorrhea is not required to make the diagnosis.²

Box 3

Criteria to establish the diagnosis of primary ovarian insufficiency

Younger than 40 years of age

Oligo/amenorrhea lasting 4 months

Two FSH levels in the menopausal range, obtained at least a month apart

Data from Nelson LM. Clinical practice. Primary ovarian insufficiency. *N Engl J Med* 2009;360(6):606–14.

Mechanisms

Primary ovarian insufficiency can be caused by follicular dysfunction or follicular depletion.²⁸ Although in follicular depletion there are no follicles left in the ovary, in follicular dysfunction even though there are follicles in the ovary they are unable to function normally. The cause of dysfunction may be a signal defect in FSH or luteinizing hormone receptor function³⁰ or G protein mutation,³¹ enzyme deficiency,³² ovarian autoimmunity,³³ or the development of luteinized graafian follicles related to low follicle cohort size.³⁴ Follicle depletion can be caused by insufficient initial follicular count, spontaneous

accelerated follicular loss as in Turner syndrome,³⁵ or environmental toxin-induced follicular loss.³⁶

Primary ovarian insufficiency can be nonsyndromic or it may be a part of a syndrome. Nonsyndromic primary ovarian insufficiency has been associated with several genes, such as bone morphogenic protein 15,³⁷ diaphanous homolog 2,³⁸ and inhibin alpha subunit.³⁹ It may also occur because of structural abnormalities in the X chromosome.⁴⁰ In 90% of cases the cause remains enigmatic.²

Evaluation

To start, take a detailed menstrual history, ask about symptoms of estrogen deficiency, and enquire about symptoms related to potentially associated diseases (Box 4). Most commonly, aberrant menstruation is the presenting complaint, although symptoms of estrogen deficiency, such as vasomotor symptoms, mood disturbances, change in sleep cycle, and dyspareunia caused by atrophic vaginitis, may be present. Primary ovarian insufficiency may also be a part of an autoimmune polyglandular syndrome; patients should be questioned and educated on symptoms of hypothyroidism and adrenal insufficiency. It may also be associated with dry eye syndrome,⁴¹ myasthenia gravis, rheumatoid arthritis, and systemic lupus erythematosus.³³ Although most cases occur sporadically, in approximately 10% to 15% of cases there is an affected first-degree relative, so a well-structured family history is important.⁴² A history of intellectual disability, dementia, tremor, or ataxia in the family may point to premutation in *FMR1* gene, responsible for fragile X syndrome, the most common form of heritable intellectual disability.⁴³ Physical examination may reveal the stigmata of associated disorders, such as autoimmune polyglandular syndrome type 1, thyroid disease, adrenal insufficiency, or Turner syndrome.

Box 4

Tests indicated in the evaluation of confirmed primary ovarian insufficiency

Karyotype (count 30 cells)

Adrenal antibodies

- 21-hydroxylase (CYP21) by immunoprecipitation
- Indirect immunofluorescence

FMR1 premutation

Pelvic ultrasound

Bone mineral density

Data from Nelson LM. Clinical practice. Primary ovarian insufficiency. *N Engl J Med* 2009;360(6):606–14.

Most patients present with secondary amenorrhea. The evaluation of amenorrhea begins with a pregnancy test. After pregnancy is ruled out a complete history should determine if the amenorrhea could be the earliest manifestation of a decline in general health, such as uncontrolled diabetes mellitus, an underlying condition, such as celiac disease, excessive exercise, inadequate caloric intake, emotional stress, or prior radiation therapy or chemotherapy. Is there galactorrhea or signs of androgen excess? It is inappropriate to attribute amenorrhea to stress without further evaluation. Indicated laboratory tests in the evaluation of secondary amenorrhea include serum prolactin, FSH, and thyrotropin levels.⁴⁴

A menopausal range FSH should be repeated in 1 month to confirm the diagnosis of primary ovarian insufficiency. After the diagnosis is confirmed the findings should be discussed with the patient at a return office visit rather than by telephone. This information is highly emotionally charged. The indicated tests to determine the mechanism of the disorder after the diagnosis of primary ovarian insufficiency is established include (1) karyotype analysis that counts 30 cells so as to uncover mosaic chromosomal abnormalities, (2) offer testing for the *FMR1* premutation, and (3) measurement of adrenal antibodies by indirect immunofluorescence and 21-hydroxylase immunoprecipitation tests.

The fragile X premutation is found in approximately 2% of women who have isolated spontaneous 46, XX primary ovarian insufficiency and in 14% of women with a familial presentation; the premutation increases the risk of conceiving a child with intellectual disability because of fragile X syndrome.⁴³ Approximately 4% of women with primary ovarian insufficiency screen positive for adrenal antibodies, which indicates that steroidogenic cell autoimmunity and lymphocytic autoimmune oophoritis are the mechanism of the disorder.⁴⁵ Ovarian antibody tests lack proved specificity and are not indicated.⁴⁶ Ovarian biopsy is not indicated in the evaluation of this condition. Because of sampling error pregnancy is known to occur even after reports of no follicles present on biopsy.⁴⁷ A pelvic ultrasound is also indicated to detect those women with primary ovarian insufficiency who have enlarged multicystic ovaries, as can be seen in 17,20-desmolase deficiency and autoimmune oophoritis.⁴⁵

MANAGEMENT

Overview

Infertility is best defined from an emotional perspective as a socially constructed life crisis.⁴⁸ Viewed from this perspective it is not primarily a medical disorder but a disruption in life plans. Evidence has demonstrated that women who have been evaluated for infertility and fail to conceive a child are twice as likely to commit suicide as women who subsequently had a child.⁴⁹ The authors' team has lived through the experience of having one of their patients with autoimmune primary ovarian insufficiency commit suicide. In the ensuing court proceedings her diary made it clear that the infertility associated with her condition was a major factor in the tragedy.⁵⁰

Primary ovarian insufficiency is a chronic disorder that not only disrupts the dreams a woman has around her fertility but the shock of the diagnosis and the stigma attached with it may leave her alone, suffering silently in grief.⁵¹ Associated medical conditions may also surface as a part of the evaluation. Women with primary ovarian insufficiency are also susceptible to future health risks of decreased bone mineral density and increased cardiovascular morbidity related to estrogen deficiency.⁵² Primary ovarian insufficiency is most commonly diagnosed as part of evaluation for other gynecologic complaints, such as irregular menses, so the diagnosis usually comes as a surprise and leaves many women with the condition feeling helpless, hopeless, and frustrated with their medical care.⁵³ Frequently the diagnosis comes after seeing more than three clinicians who did not take the menstrual irregularity seriously enough to evaluate the situation by measuring FSH.¹³ Furthermore, most women are dissatisfied with the care they receive for primary ovarian insufficiency even after the diagnosis is made.¹⁴ Most women with the diagnosis feel unprepared for the shock and want their clinician to spend more time with them to give them more information, medical guidance, and emotional support.¹⁴ These women experience emotional distress, anxiety, and depression and are longing for emotional support and professional guidance to help them find their new path forward.⁵⁴ It is crucial that clinicians provide integrative care that covers the different aspects of their health that are at risk related to the diagnosis.

Emotional Health

The diagnosis of primary ovarian insufficiency and the associated unanticipated infertility seriously disrupts life plans.⁵³ Evidence suggests that people with infertility suffer from a higher degree of psychological stress.^{48,55} Studies specifically conducted on women with primary ovarian insufficiency demonstrate lower self-esteem and increased shyness and social anxiety.⁵⁶ For many women, the grief response is equivalent to the loss of a loved one.⁵⁷ Such unexpected losses are frequently associated with increased psychological morbidity and higher rates of depression.^{58–64} Schmidt and colleagues⁶⁵ in their study showed that women with primary ovarian insufficiency had a higher frequency of depression and greater lifetime risk of depression. Thus, these women should be evaluated for underlying depression and offered expert care, should it be present. Women with primary ovarian insufficiency also have a lower perceived social support and may be isolating themselves.⁶⁶ It is important for clinicians to educate these patients and guide them to the resources that could help them in their emotional healing. If appropriate and with patient's consent, informing partners and other family members regarding the challenges these women face can help patients create an environment of trust, warmth, and support at home. When needed, community-based resources, such as couples counseling and professionally guided social services, might help in their emotional healing. The authors have found that when making the diagnosis of primary ovarian insufficiency in adolescents, taking a family systems approach is beneficial.⁶⁷

Meaning and Purpose

Maslow's hierarchy of needs is a theory that focuses on describing the stages of human growth from a developmental psychology perspective.⁶⁸ Wellness includes the psychological health that permits thriving despite the existential difficulties and challenges in life. Wellness includes such things as pursuing meaningful goals, growing and developing as a person, and establishing quality ties to others.⁶⁹ There exists what has been termed the "parental paradox." This paradox has been used as an example to describe the difference between happiness and meaning. First, in retrospect parents usually report that they are very glad they had children, but parents living with children usually score very low on happiness indicators. Raising children may decrease parental happiness but increase parental meaning in life.⁷⁰ Viktor Frankl changed Maslow's paradigm. He placed "self-transcendence" at the top of a newly ordered Maslow's hierarchy. Maslow placed "self-actualization" at the top. Frankl⁷¹ argued in his book *From Death Camp to Existentialism* that self-actualization is not possible as long as the self is the center of action. According to Frankl, one must move beyond self interest to reach the top of the human development pyramid.

For most women having children is a major life goal, and having this goal disrupted by the diagnosis of primary ovarian insufficiency is difficult and challenging. Research has shown that women with primary ovarian insufficiency who score higher on a measure of meaning and purpose have fewer symptoms of anxiety and depression, higher positive affect, and lower negative affect.⁵¹ Meaning and purpose in life is a motivational force during adversity. In a recent study women with primary ovarian insufficiency scored adversely compared with control women on all tested measures of affect. Women who had greater goal flexibility and a stronger sense of meaning and purpose in life experienced greater positive effect.⁵¹ Helping these women find new avenues to meaning and purpose may help them cope better. For many women with primary ovarian insufficiency providing spiritual care can be a path to new meaning and purpose, and likely fewer symptoms of anxiety and depression.⁷² Ventura and colleagues⁷³ provide evidence that women with primary ovarian insufficiency who scored better on a measure of spiritual well-being also scored better on a measure of functional well-being. Rearranging goals and finding strength in spiritual care can infuse patients with positive energy to move ahead and persevere.

Hormone Replacement

Most women with primary ovarian insufficiency need hormone replacement to reduce symptoms of estrogen deficiency, such as vaginal dryness and vasomotor instability. In contrast to normally menopausal women in their 50s, the need for hormone replacement in these young women clearly extends beyond the need for symptom relief. There is undoubtedly a role for continued hormone replacement until age 50 years in these young women (50 is the average age of menopause). Evidence suggests this is justified to protect them from development of serious morbidity and earlier mortality related to prolonged estrogen deficiency. Early menopause has been associated with an increased incidence of fractures and increased total mortality and mortality caused by ischemic heart disease.⁷⁴⁻⁷⁷ It is invalid to apply the results of the Women's Health Initiative to young women with primary ovarian insufficiency in determining the risk/benefit ratio for women of reproductive age. The Women's Health Initiative demonstrated that combined hormone therapy (estrogen with progestin) increased the risk of cardiovascular events in menopausal women, but importantly, the participants in this study were, on average, 63 years of age.⁷⁸ The age difference between the women in the Women's Health Initiative study and young women with primary ovarian insufficiency is of paramount import. The Women's Health Initiative was not a primary prevention study of cardiovascular disease. Such a study should have begun at the time women began developing estrogen deficiency. For many women this transition to an estrogen-deficient state could have begun 10 to 20 years before age 63. Primary ovarian insufficiency in young women is a pathologic condition in which women have lower serum estradiol levels compared with their peers of similar age; in contrast, menopause is a physiologic condition of older women.² It is important for the clinician to keep this in mind when discussing the risk/benefit ratio of hormone therapy in young women with primary ovarian insufficiency.^{2,23}

The main goal of hormone therapy for women with primary ovarian insufficiency is to mimic normal ovarian function with regard to estradiol replacement. The average serum estradiol level during the menstrual cycle in normal women is approximately 100 pg/mm.⁷⁹ Transdermal and transvaginal replacement of 100 µg/day of estradiol achieves physiologic blood levels in this range and provides adequate symptomatic relief. Transdermal or transvaginal route of administration has a lower risk of vascular thromboembolism compared with oral estrogen.⁸⁰⁻⁸² Evidence supports the addition of cyclical medroxyprogesterone acetate at the dose of 10 mg/day for 12 days each month because this guards against the potential risk of endometrial cancer by inducing full secretory endometrium and sloughing on a regular basis.^{83,84} A menstrual calendar should be maintained and a pregnancy test should be done if menses are delayed, because conception can occur in 5% to 10% of these women. Most women with primary ovarian insufficiency are experiencing ongoing intermittent ovarian function.^{2,85} If pregnancy occurs the estradiol-progestin replacement should be discontinued. Oral contraceptives are not recommended as first-line hormone replacement in women with primary ovarian insufficiency; they provide more steroid hormone than is needed for physiologic replacement and are associated with an increased risk of thromboembolic events related to the first pass effect on the liver.² A major advantage of transdermal and transvaginal estradiol replacement is the avoidance of this first pass effect on the liver.

Professional Society Recommendations

The American Society for Reproductive Medicine and the International Menopause Society have recommended estrogen-replacement therapy for women with primary ovarian insufficiency.^{44,86} There are also recommendations from several professional organizations advising that patients with primary ovarian insufficiency be offered testing for a premutation in the *FMR1* gene.⁸⁷⁻⁸⁹

Bone Health

Compared with control women, women with primary ovarian insufficiency have reduced bone mineral density.⁹⁰ No evidence-based guidelines have been developed specifically for women with primary ovarian insufficiency with regard to maintaining bone health, but it is reasonable to follow the guidelines put forth by the North American Menopause Society.⁹¹ Hypogonadism is a risk factor for osteoporosis, so patients with primary ovarian insufficiency need to be informed about this and monitored regarding their compliance with how to reduce this risk. They should be encouraged to practice a variety of weight-bearing exercises, such as walking, jogging, stair climbing, and resistance training.⁹² Intake of 1200 mg of elemental calcium per day is recommended.⁹¹ It has been recommended that adults with inadequate sun exposure take at least 800 to 1000 IU of vitamin D per day.⁹³ Adequate vitamin D status is defined as a serum 25-hydroxyvitamin D level of 30 ng/ml or higher.⁹³ Because of the uncertain effects of bisphosphonates on fetus and their long skeletal half-life these agents are not recommended in women who might subsequently conceive.⁹⁴

Genetic Health

In 10% to 15% of cases women with this disorder have an affected first-degree relative. A family history of fragile X syndrome, intellectual disability, dementia, tremor and ataxia, or symptoms like those of Parkinson's disease raises the possibility that a fragile X premutation might be the cause of the primary ovarian insufficiency. Patients with a strong family history suggesting this possibility should be offered genetic counseling before the *FMR1* test is performed. This gives them a head start in thinking about how to inform the rest of the family in the event they are found to carry the premutation.

Nutrition

An assessment by a nutritionist helps these women chart a balanced diet specific to their choices and requirements. Familiarizing them with foods rich in calcium, educating them about healthy food options to maintain cardiovascular health, and guidance about vitamin D intake are important for long-term health. Women who desire to conceive should be encouraged to get ready for pregnancy by making healthy food decisions. They should be made aware of the detrimental effects of alcohol^{95,96} and smoking⁹⁷ on the fetus and pregnancy and should be inspired to make necessary changes. Foods rich in folic acid and preconception folic acid supplements to prevent neural tube defects should be offered because pregnancy usually occurs unexpectedly in women with primary ovarian insufficiency.⁹⁸ Women with diabetes or underlying celiac disease get additional benefit from nutritional guidance.⁹⁹

Associated Conditions

Adrenal insufficiency, also known as Addison disease, is a potentially fatal disorder. One report uncovered asymptomatic adrenal insufficiency in approximately 3% of women with primary ovarian insufficiency,¹⁰⁰ an increase of at least a 100-fold risk compared with the general population. Testing for the presence of adrenal autoimmunity by measuring adrenal antibodies is recommended in all women with primary ovarian insufficiency.¹⁰⁰ Patients who test positive for adrenal autoimmunity should have an annual corticotropin stimulation test to assess adrenal function. All women with primary ovarian insufficiency should be informed about the symptoms of adrenal insufficiency and instructed to seek out evaluation should such symptoms develop.

Thyroid autoimmunity, mainly Hashimoto thyroiditis, is also more common in women with primary ovarian insufficiency; prevalence rates of 14% to 27% have been reported.^{33,101} Compared with control women, women with primary ovarian insufficiency also have an

increased incidence of dry-eye syndrome, seen in about 20% of these patients.⁴¹ Referral to an ophthalmologist can be quite beneficial. Although primary ovarian insufficiency has also been associated with other autoimmune diseases, such as myasthenia gravis, rheumatoid arthritis, and systemic lupus erythematosus, because of the limited frequency of associations testing for these and other autoimmune disorders should be based only on indication by the presence of relevant symptoms and signs.

FAMILY PLANNING

Childbearing and motherhood are celebrated by most societies and couples who electively or otherwise decide not to raise children carry a burden of stigma (Box 5).^{102–104} Even the most developed and modern societies are touched by pronatalism and pressure for reproductive conformity.¹⁰⁵ Couples facing infertility, in addition to experiencing stigma, frequently experience a sense of loss of meaning and purpose in life¹⁰⁶ and feelings of loss of control and isolation.^{107,108}

Box 5

Family planning options in primary ovarian insufficiency

- Await spontaneous conception
- Child-free living
- Adoption
- Foster children
- Oocyte donation
- Embryo donation

Data from Baker V. Life plans and family-building options for women with primary ovarian insufficiency. Semin Reprod Med 2011;29(4):362–72.

Although fertility may be a major concern for many women with primary ovarian insufficiency, it is important to point out that this is not true of all women, and certainly in many cases the diagnosis is made years before creating a family is an issue for the patient. It is important to meet the patient where she is in this regard rather than assuming that parenthood is her current goal. As one of our patients lamented after reading one of our publications,

As someone who suffers from this condition, I was happy to see mention of the emotional aspects that it involves. But I wish the medical community would stop pushing donor eggs or adoption as solutions to our problems. I understand these work for some people, but they are far from a cure. We feel lost and broken, with very little quality of life.

It is important to make clear to patients that spontaneous remission of primary ovarian insufficiency is not rare, and that unexpected pregnancy occurs in about 5% to 10% of cases.⁸⁵ Although uncommon, remissions may in some cases even last for years with return of regular ovulatory menstrual cycles.²⁸ Presently, there are no validated markers that are predictive of remission and there are no therapies proved safe and effective in restoring ovarian function and fertility in this condition. Women with primary ovarian insufficiency who wish to avoid pregnancy should not rely on the oral contraceptive. The effectiveness of these agents has not been studied in this population. There are reports of women with this condition conceiving while complying with an oral contraceptive regimen.¹⁰⁹ It is possible

that contraceptive failures occur in this population because oral contraceptives fail to adequately suppress the characteristically high serum FSH levels seen in these patients.²

It is the clinician's responsibility to assess the patient's general health with regard to the effects of primary ovarian insufficiency before helping them down the road to parenthood. For example, moving to egg donation in a woman with unrecognized major depression or asymptomatic adrenal insufficiency obviously would not be in the best interest of the woman or the child to be conceived. The appropriate time for the clinician to raise questions about creating a family, by either traditional or high-technology methods, is after having established that she is endocrinologically healthy with regard to adrenal and thyroid function and, importantly, adequately recovered emotionally from the news of the diagnosis.³

Some couples desire parenthood but are uncomfortable with adoption or reproductive technology as a solution. They are content to define their family as the couple and accept the real, albeit low, chance that they will conceive without medical intervention. Because ovarian function is intermittent and unpredictable, attempts to time intercourse are not indicated. Couples who want to optimize their chances for conception should have intercourse two or three times a week to ensure that sperm are present should an ovulation occur (sperm can survive in the female genital tract for 3 days).¹¹⁰ Although the hormone-replacement regimen induces regular menstrual cycles this does not mean that ovulation occur on Day 14 of the induced cycle. Ovulations are still intermittent and unpredictable.

For couples ready to pursue parenthood actively the options are adoption, foster parenthood, egg donation, and embryo donation. In the special circumstance in which the patient has an identical twin with normal ovarian function ovarian transplantation is possible.¹¹¹ The success of egg donations is primarily dependent on the age of the egg donor, so there is no medical urgency to proceed to egg donation. Rates of pregnancy with this method are similar among older and younger women.¹¹² There is some evidence to suggest that with egg donation there is a higher incidence of pregnancy complications, such as postpartum hemorrhage, small for gestational age, pregnancy-induced hypertension, and a minimal increase in the rate of birth malformations.¹¹³⁻¹¹⁵ However, for most couples these risks are not of a great enough magnitude to decide against the approach. Embryo donation has comparable results with egg donation and is less expensive.¹¹⁶

PLANS FOR ONGOING MANAGEMENT

Primary ovarian insufficiency is a serious chronic disease that requires ongoing management in an integrated and collaborative manner. The combination of the associated emotional sequelae including loss of meaning and purpose in life around disruption of plans for a family, need for hormone replacement, concerns regarding long-term bone health and cardiovascular health, and the potential for associated hypothyroidism and adrenal insufficiency cut across diverse sets of expertise.⁵⁰ A model of care for primary ovarian insufficiency should be developed that combines an integrative and collaborative approach in a way that patients and clinicians find satisfying.^{1,4-6}

To provide continuity of care an individual should be identified who will serve as the patient's "personal health advocate." This individual would work with the patient to develop a written ongoing management plan that integrates the diverse aspects of care these women require. The personal health advocate would assist in transition from one phase of care to another and make the necessary arrangements for care.^{117,118} For many women the most challenging part of the disorder is making decisions about their plans for creating a family in view of the diagnosis. Greil⁴⁸ has pointed out that learning of infertility precipitates a "socially constructed life crisis" that must be navigated. Primary ovarian insufficiency is one

of the special circumstances in which women may learn about their infertility even before attempting conception, sometimes even during adolescence.⁶⁷ The authors have found that including a social worker on the team adds a unique perspective and brings expertise that can link patient to community resources on wellness, individual and couples counseling, spiritual care, financial management, support groups that are professionally monitored, and generally provide a resource for finding creative solutions to unmet needs.^{119,120}

EYE TO THE FUTURE

The new paradigm for studying and treating primary ovarian insufficiency is taking a community of practice approach.¹⁰ This concept is little known in the medical community, but communities of practice have been referred to as the organizational structure of the future by the business community.⁹ The community of practice provides a construct in which stakeholders can work collaboratively to tackle complex, multidimensional, and hierarchical problems despite limited resources. Such a community of practice for primary ovarian insufficiency came together in an event organized by the National Institutes of Health.^{1,10} A major goal of the primary ovarian insufficiency community is to create a knowledge network.^{7,8} Knowledge networks disseminate ideas, catalyze creative thinking, and serve as an engine for progress and change that advance research and improve patient care. Rachel's Well, a not-for-profit entity, serves as the umbrella organization for the primary ovarian insufficiency community of practice and associated knowledge network (<http://www.rachelswell.org>).¹ The organization promotes an integrative model of care delivery and research that places the patient at the center of all efforts. Rachel's Well advocates a wellness approach to primary ovarian insufficiency. Such an approach creates synergy between the powers of spiritual care and highly technical care and requires major reorganization to a new model of research and care delivery (Figs. 1 and 2).^{6,12}

SUMMARY

Primary ovarian insufficiency is a life-altering diagnosis and many patients consider the diagnosis to be a threat to their identity as a woman. The diagnosis is much more than infertility. There are effects on emotional health, physical health, and spiritual wellness.

To make the diagnosis of primary ovarian insufficiency in a timely manner one must take oligo/amenorrhea seriously and evaluate it appropriately. Women with primary ovarian insufficiency are deficient in the ovarian hormones and estradiol should be administered by transdermal and transvaginal routes with oral medroxyprogesterone acetate.

It is important to inform women with primary ovarian insufficiency that there is a 5% to 10% chance of spontaneous conception. However, there are no proved strategies for increasing the chance of conception by improving ovarian function. Women with primary ovarian insufficiency should be encouraged to maintain a lifestyle that optimizes bone and cardiovascular health.

The emotional shock of the diagnosis can be severe and it takes time for husband and wife to get on the same page about next steps. Some time to permit natural conception to occur while they process the grief is usually in order. The amount of time needs to be individualized, but in view of the level of grief that can be encountered 3 years of processing before moving forward seems reasonable. Setting a time such as this before moving forward with creating a family takes the pressure off and permits a measured and informed approach to next steps. Some decide to be the completed family together as a couple without children. If no spontaneous conception occurs in the allotted adjustment time interval, adoption, foster children, egg donation, and embryo donation are the options for those who want to be parents.

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KEY POINTS

- Most women with primary ovarian insufficiency come to clinical attention with oligo/amenorrhea. Take this sign seriously, evaluate it properly, and avoid delay in diagnosis.
- The proper laboratory evaluation of amenorrhea includes a pregnancy test, and if negative, measurement of serum FSH, prolactin, and thyrotropin.
- Women younger than 40 who have 4 months of oligo/amenorrhea and two menopausal serum FSH levels, 1 month apart, meet criteria for primary ovarian insufficiency.
- The indicated tests to determine the mechanism of the disorder include:
 - Karyotype analysis that counts 30 cells so as to uncover mosaic chromosomal abnormalities.
 - Testing for the *FMRI* premutation.
 - Measurement of adrenal antibodies by indirect immunofluorescence and 21-hydroxylase immunoprecipitation tests.
- Primary ovarian insufficiency is a life-altering diagnosis that is highly emotionally charged. Inform women in the office; be supportive and sensitive to their emotions.
- Primary ovarian insufficiency is more than infertility. Physical and emotional health need to be addressed before moving on to plans for creating a family.



Fig. 1.

Chronic illnesses create burdens for patients and their caregivers. They also restrict life and create uncertainty about the future. Successful interventions to reorganize research and care delivery in chronic diseases share common characteristics as illustrated. (*Data from Wagner EH, Austin BT, Von Korff M. Organizing care for patients with chronic illness. Milbank Q 1996;74(4):511–44.*)

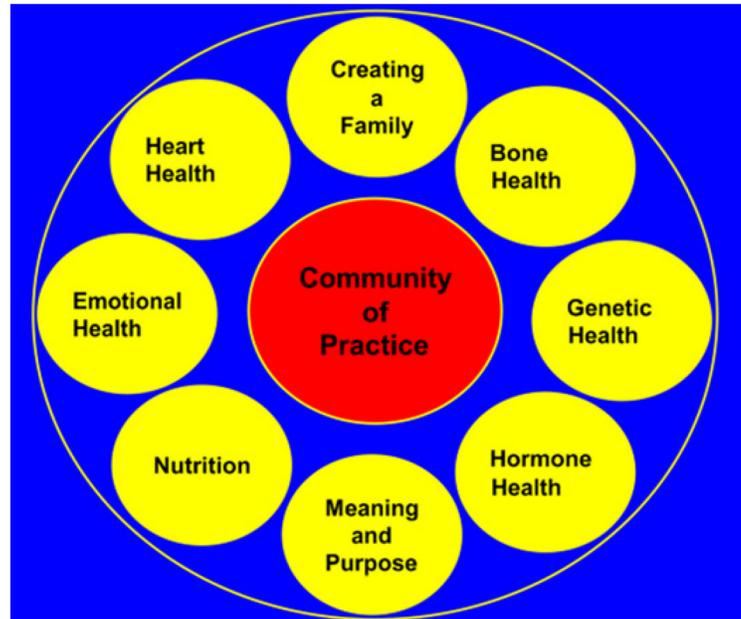


Fig. 2.

The large circle defines the domain of the community of primary ovarian insufficiency. This includes all women with primary ovarian insufficiency that at any one time may be focused on entirely different aspects of their chronic disease. The disorder is much more than infertility. The red circle in the center represents the community of practice that serves these women. A community of practice is a group of people who provide services to the larger community. By sharing information and experiences with each other they develop personally and professionally, and can provide better care to the larger community.