Consensus of the Fragile X Clinical & Research Consortium on Clinical Practices

Fragile X-associated Primary Ovarian Insufficiency (FXPOI)

First Issued: June 2011
Updated: October 2012

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Introduction

Fragile X-associated primary ovarian insufficiency (FXPOI) is one of the fragile X-associated disorders that can affect some premutation carriers. Primary ovarian insufficiency (POI) refers to a spectrum of impaired ovarian function that includes cessation of menses prior to the age of 40 years. The terminology has evolved, and although both premature ovarian failure (POF), and premature menopause have been widely used, they are no longer thought to be as accurate as POI.

There are no standardized diagnostic criteria for POI, but a practical definition is four or more months of "disordered menses" in association with menopausal FSH levels, in a woman prior to the age of 40 years (Nelson, 2009). The difference from menopause is that there is varying and unpredictable ovarian function in 50% of women diagnosed with POI, and 5-10% of those women go on to conceive a viable pregnancy following their diagnosis (Rebar, 1990). Approximately one in 100 women in the general population develops POI, whereas approximately 20% of women who carry the *FMR1* premutation develop the condition (Sherman, 2000). This risk depends, in part, on repeat length: the highest risk appears to be for women carrying premutation alleles in the 80-100 CGG repeat range (Allen et al., 2007, Ennis et al., 2006; Sullivan et al., 2005). Premutation carriers of all ages should inform their primary care physician or gynecologist of their general risk for POI in order to facilitate recognition of early signs and better management. All women presenting with POI should be tested for the *FMR1* premutation regardless of their family history (ACOG, 2010).

Clinical Features

Signs and symptoms of POI include intermittent and unpredictable menses, with eventual early cessation. Approximately one-third of women with FXPOI, equivalent to 7% of premutation carriers, experience final cessation of menses at or before age 29 years (De Caro et al., 2008). Age at menarche and primary amenorrhea do not appear to be associated with FXPOI. Three percent of premutation carriers will have cycle irregularities in their teens or twenties, and 1% of premutation carriers will have cessation of menses prior to age 18 years (De Caro et al., 2008). Symptoms of estrogen deficiency include hot flashes, night sweats, vaginal dryness, and dyspareunia. Estrogen deficiency also leads to reduced bone mineral density and osteoporosis. Thyroid problems, depression and anxiety may be present at increased rates in premutation carriers with FXPOI compared to both premutation carriers without FXPOI, and non-carriers (Hunter et al., 2010). Autoimmune disorders are known to be associated with POI in the general population (Nelson, 2009), and are also being recognized in *FMR1* premutation carriers (Coffey et al., 2008), but it is not yet known whether they are increased specifically in women with FXPOI.

Diagnosis

Increased levels of serum follicle-stimulating hormone (FSH) levels in the menopausal range, on two occasions one month apart, along with reduced serum estradiol levels are diagnostic of FXPOI in a woman with a known *FMR1* premutation. Reduced levels of anti-mullerian hormone (AMH) levels can also provide a more sensitive indication of decreased ovarian reserve in earlier stages of POI, and may be useful as a screening tool (Rohr et al., 2008). However, in a known premutation carrier female it should not be presumed that irregular menses is a result of FXPOI. Initial investigations should also include a pregnancy test, serum prolactin level, and thyroid hormone levels. Additional investigations could be undertaken depending on clinical suspicion, e.g. a karyotype to rule out Turner syndrome, and measurement of Gal-1-P to rule out galactosemia.

Therapeutic Strategy

At this time, there are no successful therapies to regain ovarian function for women with FXPOI. Management strategies are supportive and expectant. The following discussion of management issues is summarized from Nelson's excellent review of POI in the *New England Journal of Medicine* (2009).

1. Emotional well-being. A diagnosis of POI can be devastating to a woman who has not completed, or even started, family planning. Even for a woman who was not planning a pregnancy, the loss of fertility can lead to emotional distress. Health care providers should attend to the psychological impact of this diagnosis and provide appropriate support and resources. Furthermore, women with the *FMR1* premutation may be at increased risk for depression and anxiety, and unexpected infertility could be a trigger for clinically significant mental health issues. A follow-up visit to screen for symptoms of depression and anxiety is suggested.
2. Hormone Replacement Therapy (HRT). The American Society for Reproductive Medicine and the International Menopause Society recommend estrogen replacement therapy for women with POI (2004; Pines et al., 2007). Transdermal estradiol 100 micrograms per day is recommended over oral options, as it effectively treats symptoms and is associated with a lower risk of venous thromboembolism (Canonico et al., 2007). Cyclic medroxyprogesterone acetate 10 mg per day for 12 days per month is recommended for protection against endometrial cancer. Oral contraceptives exceed physiologic requirements and are not recommended as first-line management. At the age of 50, the risks and benefits of HRT should be reevaluated. The Women's Health Initiative study found an increased risk of adverse cardiovascular events in women on HRT who were post-menopausal with an average age of 63 years (Rousseau et al., 2002). These risks have not been generalized to younger women with POI.

3. Bone mineral density. General guidelines to minimize bone loss include weight-bearing physical activity and intake of a healthy balanced diet. Adequate vitamin D status is recommended, indicated by a serum 25-hydroxyvitamin D level of 30 ng/ml (75 nmol/L). Supplementation of 800-1000 IU of vitamin D, three per day, is suggested for all adult women who do not receive significant sun exposure (Holick, 2007). Calcium supplements increase bone mineral density, but do not reduce the risk of fractures, and may increase the risk of myocardial infarction (Bolland et al., 2010). Bone mineral density should be measured at diagnosis, and follow-up depends on the result. A normal densitometry scan need not be repeated for a minimum of two years. If osteoporosis is diagnosed, there are effective treatments (including bisphosphonates) that should be implemented.
4. Family planning. Women with FXPOI should not assume infertility, and contraception is recommended for those not wanting to conceive a pregnancy. Barrier methods of contraception or intra-uterine devices are recommended over oral contraceptives, which have reduced effectiveness in the context of POI in the general population (De Caro et al., 2008). A menstrual diary is advised, with prompt pregnancy testing in the case of late menses. For women wanting to conceive, there is a 5-10% chance of pregnancy in POI in the general population, but it is not known whether this figure applies to FXPOI as well. Parenthood options include a "wait and see" approach for the chance of a natural conception, adoption or assisted reproductive technologies using egg donation or embryo adoption. Future options may include "emergency" IVF with embryo storage (Michaan et al., 2010) and egg harvesting and cryopreservation (Ezcurra et al., 2009). These procedures are currently offered in some facilities, though they are still in evolution. They are not yet considered to be mainstream and have uncertain efficacy.

Additional Resources

National Fragile X Foundation: www.fragilex.org/fragile-x-associated-disorders/fxpoi/
International Premature Ovarian Failure Association: www.pofsupport.org

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Author note: This guideline was authored by Gudrun Aubertin, MD and reviewed and edited by consortium members both within and external to its Clinical Practices Committee. It has been approved by and represents the current consensus of the members of the Fragile X Clinical & Research Consortium.

Funding: This project was made possible by Cooperative Agreement U01DD000231 from the Centers for Disease Control and Prevention to the Association of University Centers on Disabilities (AUCD) and RTOI 2008-999-03 from AUCD to W.T. Brown in support of the National Fragile X Clinical and Research Consortium. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

The Fragile X Clinical & Research Consortium *was founded in 2006 and exists to improve the delivery of clinical services to families impacted by any Fragile X-associated Disorder and to develop a research infrastructure for advancing the development and implementation of new and improved treatments. Please contact the* ***National Fragile X Foundation*** *for more information. (800-688-8765 or www.fragilex.org)*