NATIONAL **FRAGILE X** FOUNDATION
FRAGILE X CLINICAL & RESEARCH CONSORTIUM

Consensus of the Fragile X Clinical & Research Consortium

Fragile X-Associated Primary Ovarian Insufficiency (FXPOI)

Also referred to as Fragile X Premature Ovarian Insufficiency

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Fragile X-Associated Primary Ovarian Insufficiency

Introduction

Fragile X-associated primary ovarian insufficiency (FXPOI) is one of the Fragile X premutation-associated conditions and is the most frequent single gene cause of primary (also called premature) ovarian insufficiency (POI).[1] There is a spectrum of ovarian function, and POI is diagnosed when ovarian reserve markers are very reduced, although women may still be having irregular menstrual cycles. The diagnosis requires 1) at least four months of absent menstrual periods before age 40 and 2) a single serum follicle-stimulating hormone (FSH) level in the menopausal range >25 IU/L (international units per liter).[2]

The POI terminology has evolved, and although both the terms “premature ovarian failure” (POF) and “premature menopause” have been used, with our current understanding of the disease process, they are no longer as scientifically accurate as the term premature ovarian insufficiency (POI). Importantly, there are differences between menopause and POI besides the age of the woman. About 50% of women diagnosed with POI have some varying and (but unpredictable) ovarian function. Indeed, about 5% to 10% of women with POI go on to conceive a viable pregnancy following their diagnosis.[3]

About 20% of women who carry a Fragile X premutation over their reproductive lifespan develop POI, compared with only 3%–4% in the general population.[1, 2] Not all women with a premutation will experience symptoms of FXPOI; thus, identifying risk factors to predict the onset of FXPOI is imperative for women’s health. Women who carry a Fragile X premutation should inform their primary care physician or gynecologist of their increased risk for POI in order to facilitate recognition of early symptoms and better management. All women presenting with POI should be tested for the Fragile X premutation, regardless of their family history.[2,4] Despite these guidelines, many women with FXPOI have reported challenges with receiving a diagnosis from their healthcare providers.[5] In fact, a survey of women’s healthcare providers found limited FXPOI knowledge,[6] confirming the reports of women having to provide educational materials to their providers.[5]

FXPOI Clinical Features

Women with a premutation, even those who do not develop FXPOI, exhibit some signs of diminished ovarian reserve. Women with a premutation, on average, experience natural menopause five years earlier than women without a premutation.[7] When compared to women without a premutation, women with a premutation have lower ovarian reserve across all ages.[8,9] The premutation effect on the ovaries can also happen very early; approximately 3% of women who carry the premutation will have menstrual cycle irregularities in their teens or twenties due to FXPOI, and 1% of women who carry the premutation will stop having periods prior to age 18 years. About one-third of women with FXPOI, equivalent to 7% of women who carry the premutation, stop having periods at or before age 29 years.[10]

Early estrogen deficiency is a consequence of POI. Symptoms of estrogen deficiency include hot flashes or flushes, night sweats, vaginal dryness, and painful intercourse, all of which have a significant negative impact on a woman's quality of life. Estrogen deficiency also leads to other medical morbidity, including reduced bone mineral density, osteoporosis, earlier-onset cardiovascular disease, and dementia.[11-14] A woman with a premutation may experience co-occurring conditions with FXPOI. There are other conditions unrelated to estrogen exposure that may be experienced at a higher frequency among women with a premutation, including thyroid disorders, depression, anxiety, fibromyalgia, migraine headaches, and hypertension (reviewed in[15]). Specific autoimmune disorders are known to be associated with certain causes of POI and are also being recognized in women who carry the Fragile X premutation.[16,17] It is not yet known whether autoimmune disorders are increased specifically in women with FXPOI.

FXPOI Risk Prediction

As noted above, not all women with a premutation experience FXPOI. One well-documented risk factor is the premutation repeat size: the highest risk for ovarian dysfunction is for women carrying premutation alleles in the 80–100 CGG repeat range, not the highest alleles of >100 repeats. (Although these group ranges are not exact.)[8,9,18-22] One study estimated the risk of FXPOI to be 38% in this high-risk group,[20] although more studies are needed to better define high-risk alleles and the reason for this non-linear association. Irrespective, most premutation carriers have at least a small increased risk above that found in the general population,[8,9]

although, a recent study found that individuals with 55–69 or >120 repeats did not have a significantly increased risk for FXPOI compared to women with <45 repeats.[22] No significant relationship was found between AGG interruptions within the CGG repeat and the risk for FXPOI.[23] Smoking is another known risk factor that decreases age at menopause. This is true for all women, not just women who carry the premutation.[20] Lastly, data suggest that other genes may modify the age of onset for FXPOI, those that may or may not interact directly with FMR1.[7-9,24,25] More work is being done to identify these genes.

FXPOI Diagnosis

Absent menses for at least four months, along with a menopausal level of serum FSH (>25 IU/L), are diagnostic of FXPOI in a woman with a known Fragile X premutation younger than 40 years of age.[2] There is no set pattern, however, to the menses; they can stop abruptly permanently or come and go at irregular intervals for years. Reduced levels of anti-Müllerian hormone (AMH) can also provide an indication of decreased ovarian reserve (or impaired ovarian responsiveness) in earlier stages of POI and may be useful as a screening tool.[8,9,26] Low AMH, however, is not diagnostic of POI since women can continue to have regular cycles for years with an undetectable AMH. Even when a woman is a known carrier of a premutation, it should not be presumed that irregular menses are a result of FXPOI. Other diagnoses that should be considered include pregnancy, polycystic ovarian syndrome, hypothalamic amenorrhea, endocrine disorders (such as thyroid disease or hyperprolactinemia), and structural uterine causes. If a woman has POI but is not a carrier of a Fragile X premutation, there are several other causes for POI that should be investigated, including Turner syndrome or POI associated with adrenal autoimmunity. A typical POI work-up includes DNA testing for Fragile X premutation, karyotype (non-Fragile X chromosome analysis), thyroid studies, and adrenal autoimmune studies.[2]

Therapeutic Strategy

At this time, there are no clinically established successful therapies to regain ovarian function for women with FXPOI. However, there are important strategies to minimize the medical and emotional consequences associated with ovarian insufficiency. The following discussion of

management issues is summarized from Nelson's review of POI in the New England Journal of Medicine (2009).

1. **Emotional well-being.** A diagnosis of POI can be emotionally devastating for 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. Healthcare providers should attend to the psychological impact of this diagnosis and provide appropriate support and resources. Furthermore, women with the premutation may be at increased risk for depression and anxiety. The prospect of the associated infertility may trigger clinically significant existential and mental health issues. A follow-up visit to screen for symptoms of depression and anxiety and providing appropriate referrals is recommended.

2. **Hormone Replacement Therapy (HRT).** HRT is recommended for women with POI for a variety of reasons. Foremost, bone density continues to accrue during the 20s and 30s, peak bone mass is an important concern for women with POI. Women with POI who do not take HRT have a very high risk of developing osteoporosis.[11] Published 2024 guidelines recommend a bone mineral density scan at time of diagnosis of POI.[2]

   There are also higher risks of cardiovascular disease and all-cause morbidity in women with POI, such that not taking HRT is associated with reduced life expectancy.[2]

   The American College of Obstetricians and Gynecologists and the North American Menopause Society recommend hormone replacement therapy.[27,281,2] (HRT)[3]) for women with POI who do not have contraindications. Based on interviews with 79 women who carry a Fragile X premutation, more than half had suboptimal HRT use; the majority reported their doctor never mentioned HRT or advised them against using HRT.[29] Thus, there needs to be increased awareness of the benefits of HRT for women with FXPOI. As noted by others,[30,31] the conclusions of the Women's Health Initiative,[32] which was conducted in older women, do not extend to young women with POI. There is an age window during which HRT is beneficial, and its use is recommended until the median age of natural menopause.[28]

Estradiol is the prominent estrogen in women of reproductive age. When measured across the entire menstrual cycle, the average serum estradiol level is about 100 pg/mL.[33] The 100 micrograms (mcg) per day estradiol patch and vaginal ring deliver the appropriate amount of estradiol each day to maintain systemic levels in this range.

Transdermal (patch or gel) or transvaginal estradiol 100 mcg per day is recommended over oral options, as these effectively treat symptoms and are associated with a lower risk of venous thromboembolism.[34] Some women prefer to take HRT orally despite the increased risk of thromboembolism. In this case, oral estradiol in a dose of 2 mg per day would supply the equivalent estrogen effect and is generally well tolerated. Estradiol is preferred over other estrogen formulations, including conjugated equine estrogen. Uterine endometrial protection is critical for any patients taking estrogen to prevent hyperplasia and endometrial cancer. This can be provided via oral progesterone (e.g., medroxyprogesterone acetate 10 mg by mouth per day for 10 days per month) or with a levonorgestrel intrauterine device.

Oral contraceptive pills can be used for hormone replacement therapy, but there have been no randomized trials that compare oral contraceptive pills to hormone therapy as described as above. Oral contraceptive pills are more potent and may not be as effective in supporting bone health. There have been some small studies that showed hormone therapy is superior at improving and maintaining bone density as compared to oral contraceptive pills.[35,36] A prospective three-year randomized controlled trial showed that young women (< 42 years old) with POI can restore their bone density to normal within three years of beginning the recommended regimen of physiologic HRT.[37] The women with POI in this study on the recommended regimen of physiologic transdermal estrogen and oral progestin replacement (average age of 33 years) had a 7.7% gain in femoral neck BMI. These women were able to fully recover bone density despite the fact they experienced years of estradiol deficiency prior to establishing peak bone mass.

As noted above, in interviews with women carrying a premutation,[29] revealed that a proportion of women, and in some cases their physicians, did not appreciate the

importance of HRT in young women with POI. Thus, each woman should openly voice her questions or concerns about HRT and discuss alternatives and risks with her physician to identify her best option for care. At the age of 50, the risks and benefits of HRT should be reevaluated.

3. **Bone mineral density.** General guidelines to minimize bone loss include weight-bearing physical activity and intake of a healthy balanced diet. The recommended dietary allowance (RDA) for calcium is 1000 mg per day for women 19–50 years old and 1300 mg per day for girls 9–18 years old. Obtaining adequate calcium through food is preferred over supplements because of the additional nutrients that are in dairy products. 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 per day is suggested for all adult women who do not receive significant sun exposure.[38] Calcium supplements increase bone mineral density, but may not reduce the risk of fractures, and may increase the risk of myocardial infarction.[39] Bone mineral density should be measured at the time of diagnosis of POI, and follow-up depends on the result. Bisphosphonates are not recommended in young women with POI because of potential embryo toxic effects in the event of a subsequent unexpected pregnancy.[16] As mentioned above, on the appropriate regimen of physiologic HRT up to the typical age at menopause (~50 years of age), bone mineral density can return to normal in women with POI. It is expected that women with FXPOI should respond similarly, although no clinical trial has been done.

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 may have reduced effectiveness in the context of POI.[40] A menstrual diary is advised, with prompt pregnancy testing in the case of late menses.

   There are several parenthood options available to women with FXPOI, depending on each woman's fertility and family planning goals. When a woman is diagnosed with FXPOI, a referral to a genetic counselor is indicated to discuss the risks of transmission

of the Fragile X pre or full mutation to offspring and risk of Fragile X-related conditions in other family members. Some women may want to take a "wait and see" approach for the chance of a natural conception while on HRT, which is known to effectively reduce serum LH levels. The amount of time to use this approach depends on each woman's situation. As noted above, women with POI have a 5%–10% lifetime chance (or risk) of pregnancy due to intermittent ovulatory activity.[41,42] This rate may be higher (about 13%) in women with FXPOI.[29] There are no fertility treatments that are effective, however, at ovulation induction once someone has been diagnosed with POI. When comparing hormone replacement therapies, there is a theoretical benefit of taking estradiol with cyclic progesterone over oral contraceptive pills. Oral contraceptive pills negatively affect the cervical mucus and can thin the endometrial lining of the uterus, both of which could impede conception.

Physiologic HRT has the advantage of lowering serum luteinizing hormone levels to normal in women with POI, which theoretically could improve their chance of normal follicle growth and subsequent ovulation.

Some women may choose fertility treatment, such as in vitro fertilization (IVF), especially if looking to pursue preimplantation genetic testing (PGT). However, fertility treatment with a woman's own eggs has very low chances of success once POI has been diagnosed due to the severe diminished ovarian reserve. Some women choose adoption. Some women proceed with other assisted reproductive technologies using egg or embryo donation. All options should be discussed with a woman diagnosed with FXPOI.

For women who are carriers of Fragile X and at risk of FXPOI, a referral to a reproductive endocrinologist can be very helpful. Some women will opt to proceed with fertility preservation at a young age, e.g., mature oocyte cryopreservation. Having oocytes cryopreserved allows a woman to go through fertility treatment in the future, when she is ready to have children, but when her fertility may be severely diminished.

Additional Resources

Guideline on Premature Ovarian Insufficiency (*European Society of Human Reproduction and Embryology*)

FXPOI: What Do I Need to Know? Webinar with Dr Amanda Vincent MD, 17 March 2025

The latest information on premature ovarian insufficiency and FXPOI. Dr Vincent is a board member of the International Menopause Society and co-chair of the International POI Guideline Development Group.

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About the FXCRC: The National Fragile X Foundation's Fragile X Clinical & Research Consortium was founded in 2006 and exists to improve the delivery of clinical services to families impacted by Fragile X 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 at 800-688-8765 or fragilex.org.