

FRAGILE X INFO SERIES: FRAGILE X-ASSOCIATED PRIMARY OVARIAN INSUFFICIENCY (FXPOI)

Overview

Fragile X is a group of conditions associated with changes in the Fragile X gene – called FMR1 and located on the X chromosome. The FMR1 gene can undergo changes, when inherited, which affects a pattern of DNA called CGG repeats. Typically, the FMR1 gene has up to 54 CGG repeats, though the range between 45 – 54 repeats, is called the intermediate or gray zone. A premutation carrier has 55–200 CGG repeats, and someone with a full mutation has more than 200 CGG repeats.

When a premutation or full mutation is present, it can result in a Fragile X-associated Disorder (FXD). These include:

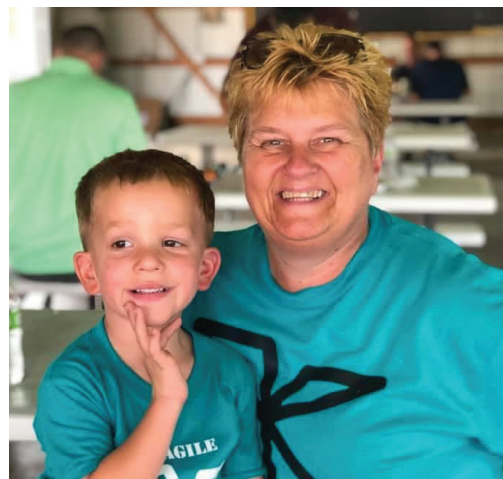
- Fragile X syndrome (FXS): A condition affecting intellectual, behavioral, and social development. It occurs in both males and females who have a full mutation of the FMR1 gene.
- Fragile X-associated tremor/ataxia syndrome (FXTAS): An adult onset (over 50 years of age) neurological condition, seen in males and females, but more common and more severe in some male premutation carriers. It can cause tremors, memory, and balance issues.
- Fragile X-associated primary ovarian insufficiency (FXPOI): A condition affecting ovarian function that can lead to infertility and early menopause in some female premutation carriers.
- Other issues may be present in premutation carriers, and this is an ongoing area of study for researchers.

General

- The number of individuals in the U.S. who have or are at risk for a premutation-associated condition ranges from 1 in 151 females, or about 1 million women, to 1 in 468 males, or about 350,000 men.
- The fragile X premutation (PM) is the most frequent single gene cause of primary ovarian insufficiency (POI). POI is a spectrum condition and is diagnosed when indicators of ovarian function are reduced and show an impaired response, although women may still be having menstrual cycles
- About 20% of women who carry a fragile X premutation over their reproductive life span develop POI, compared with only 1% in the general population.
- Women with a premutation may not experience symptoms of FXPOI; thus, identifying risk factors to predict 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

FXPOI Statistics

- Women with a premutation, on average, experience natural menopause at an earlier age compared to those without a premutation—the mean age of natural menopause being reduced by about 5 years from the typical age of about 51 years.
- Early estrogen deficiency is a consequence of POI. Symptoms of estrogen deficiency include hot flashes/flushes, night sweats, and vaginal dryness.
- Estrogen deficiency also leads to reduced bone mineral density, osteoporosis, a higher risk for earlier-onset cardiovascular disease and dementia.
- A woman with a premutation may experience co-occurring conditions with FXPOI. More evidence is required to determine whether the following conditions are experienced at a higher frequency among women with a premutation: thyroid disorders, depression, anxiety, fibromyalgia, migraine headaches, and hypertension.



Risk for FXPOI

- 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.
- Though all premutation carriers have at least a small increased risk above that found in the general population

Diagnosis of FXPOI

- Unpredictable or absent menses for 4 months along with menopausal levels of serum FSH, on two occasions one month apart, are diagnostic of FXPOI in a woman with a known fragile X premutation.
- Even when a woman is a known carrier of a premutation, it should not be presumed that irregular menses are a result of FXPOI.

Interventions and Treatments

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 clinical and emotional consequences associated with ovarian insufficiency.

- 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.
- Hormone Replacement Therapy (HRT). Given that bone density continues to accrue during the 20s and 30s, peak bone mass is an important concern for women with POI. The American Society for Reproductive Medicine and the International Menopause Society recommend hormone replacement therapy (HRT) for women with POI.
- Bone mineral density. General guidelines to minimize bone loss include weightbearing physical activity and intake of a healthy balanced diet.
- Family planning. Women with FXPOI should not assume infertility, and contraception is recommended for those not wanting to conceive a pregnancy.
- Parenthood. There are several parenthood options available to women with FXPOI, depending on the needs of the woman.

Notes:

- For women with FXPOI (those confirmed to be premutation carriers), each child will have a 50% chance of receiving the FMR1 mutation, with the potential of their premutation expanding to a full mutation (>200 CGG repeats).
- Women with FXPOI **do not** have an increased risk of FXTAS compared with women who carry premutations and have normal ovarian function.

International Fragile X Premutation Registry. For individuals with the premutation and their families. The registry will help advance research into the premutation condition. Learn more at fragilex.org/ifxpr.

About the NFXF

The National Fragile X Foundation (NFXF) was founded in 1984 to support individuals with Fragile X syndrome (FXS), their families, and the professionals who work with them. Today, it is a comprehensive resource not only for FXS, but also for the conditions of Fragile X-associated tremor/ataxia syndrome (FXTAS), Fragile X-associated primary ovarian insufficiency (FXPOI), and other premutation carrier conditions and disorders. The NFXF is dedicated to serving the entire Fragile X community to live their best lives by providing the knowledge, resources, and tools, until, and even after more effective treatments and a cure are achieved. Learn more at <https://fragilex.org/welcome>

If you have questions please reach out to us at treatment@fragilex.org or call (800) 688-8765.

Resource:

Consensus of the Fragile X Clinical & Research Consortium - Fragile X-associated Primary Ovarian Insufficiency (FXPOI) - https://fragilex.org/wp-content/uploads/2018/11/FX_PrimaryOvarianInsufficiency_Consensus_Document.pdf

Reproductive Options - <https://fragilex.org/understanding-fragile-x/fragile-x-101/premutation-carriers/reproductive-options/>

