

Editor's Note: The NFXF was honored to be part of the first-ever "FMR1 Premutation and Premature Ovarian Failure" meeting convened by Dr. Nelson last October in New Orleans. Representatives from the medical and genetic counseling fields met to plan ways to spread awareness, increase the diagnoses and provide appropriate counseling regarding this condition. As part of that process, in 2007, the NFXF will be mailing a POF informational postcard to every OB/GYN in the United States.

Lawrence M. Nelson, MD

Menstrual Cycles, the FMR1 Premutation, and "Primary Ovarian Insufficiency"

What does the menstrual cycle have to do with Fragile X? More than many people might think.

The Fragile X community continues to grow and to encompass an ever broader spectrum of individuals and disorders. Now this community includes women who are experiencing irregular menstrual cycles—and the gynecologists who evaluate and treat them.

I am a gynecologist who has joined the Fragile X community because of my research involving a condition known as "premature ovarian failure" (POF). (At one time it was also called "premature menopause.") For reasons I will outline below, I am now proposing that we consider changing its name again to "primary ovarian insufficiency."

POF describes a condition that causes young women to cease having menstrual periods and to develop other symptoms of menopause such as hot flashes, vaginal dryness and infertility. Menopause, however, is defined as the permanent cessation of menstrual periods, and it occurs at an average age of 50.

We now know that in contrast to what happens in menopause, young women with premature ovarian failure face a more complex set of circumstances. It has been repeatedly demonstrated that they can sometimes experience the return of menstrual periods and even get pregnant many years after the POF diagnosis. That is why I think a better term for this condition is "primary ovarian insufficiency." Actually, this term was first used by Fuller Albright in a publication in 1942. He is considered by many to be the father of modern endocrinology, so the term has a rich pedigree. I want to revive it.

Normal ovarian function is required in order for women to experience regular menstrual cycles. The ovary is more than a reproductive organ that releases eggs. The ovary also releases the hormones estrogen and progesterone into the

circulation in a cyclic manner. This results in a normal regular menstrual pattern. When the menstrual cycles fail to come regularly it may mean that the ovaries are not functioning normally. Research has demonstrated that abnormalities in

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the *FMR1* gene, the gene responsible for fragile X syndrome, can be associated with problems in ovarian function.

The world of genetics is changing. There was a time when the thinking went something like this: "One gene has one function, and a malfunction in this gene will cause one disorder."

The *FMR1* gene clearly demonstrates the fallacy in this approach. It turns out

that abnormalities in the *FMR1* gene can cause problems in at least two ways: 1) it can be less active than normal and cause fragile X syndrome, or 2) it can be more active than normal and cause other disorders.

In its fully mutated state (more than 200 CGG repeats), the *FMR1* gene is turned off and thus fails to make an important protein that is needed for normal brain development. This causes fragile X syndrome. In the past it was thought that those carrying a premutation in the *FMR1* gene (55 to 200 CGG repeats) were not at risk for any disorders. We now know that this is not the case.

It turns out that a premutation in *FMR1* causes the gene to make abnormally increased amounts of messenger RNA. This can be toxic to certain brain cells and lead to the development of FXTAS (fragile X-associated tremor/ataxia

syndrome), which can cause dementia in older adults. A similar toxic mechanism might impair ovarian function. This could explain why some women who carry the *FMR1* premutation develop problems with their menstrual cycles.

Girls and young women who are known to carry the *FMR1* premutation should be informed about the potential adverse effects on their ovarian function, their menstrual cycles, and their fertility. They need know what is considered normal, and when to seek evaluation of menstrual abnormalities.

In my view it is a good idea for all girls and young women to get in the habit of keeping a menstrual calendar. This is especially pertinent for those who have a premutation in *FMR1*, since they are at increased risk of menstrual cycle irregularity. Girls normally experience their first menstruation by age 15. Failure to begin by then should be evaluated, as it could be a sign that the ovaries are not working properly. While some irregularity is to be expected during the first year of menstruation, once girls have had their first period it is abnormal for them to go for three months or more without one. Teens or adult women who experience that long an interval need evaluation.


In adult women periods normally commence every 21 to 35 days, with 28 days as the average. This interval is determined by counting from the start of one period to the start of the next. A failure to experience a normal regular menstrual pattern within these limits could be a sign of

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impaired ovarian function.

Most of my patients with premature ovarian failure have experienced a delay in the diagnosis of their condition because abnormalities in the pattern of their menstrual cycles were not taken seriously. A delay in this diagnosis means more time in an estrogen-deficient state, which is not normal or desirable for teenage girls and young women. In the long term, this

estrogen deficiency could translate into reduced bone density and an increased risk for osteoporosis.

The menstrual cycle requires consistent monitoring, with a normal cycle indicating that the ovaries are working properly. If cycles are not normal, an effort should be undertaken to find out why. From this perspective, one might say, "The menstrual cycle is a vital sign." 

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have revealed that they too exhibit excessive protein synthesis upon mGluR5 activation, and show alterations in the protein synthesis machinery. Indeed, our research continues to uncover evidence that FXS is a disorder of excessive Gp I mGluR

signaling, and we continue to discover more about the molecular mechanisms involved. We are hopeful that these studies will demystify the mechanisms of FXS, and lead to specific, effective treatments and diagnostics in the not-too-distant future. 