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

Consensus of the Fragile X Clinical & Research Consortium

FRAGILE X-ASSOCIATED PRIMARY OVARIAN INSUFFICIENCY

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Introduction

Fragile X-associated primary ovarian insufficiency (FXPOI) is one of the fragile X premutation- associated disorders. In fact, the fragile X premutation (PM) is the most frequent single gene cause of primary ovarian insufficiency (Sherman 2000). POI is a spectrum and is diagnosed when indicators of ovarian function are reduced and show an impaired response, although women may still be having menstrual cycles (Welt 2008). "Overt" POI is diagnosed when a woman has 1) experienced at least 4 months of unpredictable or absent menstrual periods before age 40 and 2) has two serum follicle stimulating hormone (FSH) levels in the menopausal range as defined by the laboratory determining the measurement (Nelson 2009). "Occult POI is diagnosed when a woman has normal FSH and regular menses, but reduced fertility. "Biochemical" POI is diagnosed when FSH is elevated and the woman has regular menses and reduced fertility (Nelson 2009). Another term used for biochemical POI is "diminished ovarian reserve (DOR)", although it is not as scientifically accurate. The term DOR is a clinical term used to describe a situation in which a woman does not respond well to fertility medications.

We use the term POI to indicate overt POI unless specifically stated otherwise. The terminology has evolved, and although both 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 POI. Importantly, there are differences between menopause and POI besides the age of the woman. About 50% of women diagnosed with POI have varying and unpredictable ovarian function. Indeed, about 5 to 10% of women with POI go on to conceive a viable pregnancy following their diagnosis (Hipp et al., 2016; Rebar 2009).

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. Thus, there is at least a 20-fold increased risk for POI among women with a premutation. It must be remembered, however, that 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 (ACOG 2010).

Clinical Features

Evidence shows 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 (Allen et al., 2014). 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 (De Caro et al., 2008). 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 (De Caro et al., 2008).

Early estrogen deficiency is a consequence of POI. Symptoms of estrogen deficiency include hot flashes/flushes, night sweats, vaginal dryness and painful intercourse. 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 (reviewed in (Wheeler et al., 2014)). Specific autoimmune disorders are known to be associated with certain causes of POI (Nelson 2009) and are also being recognized in women who carry the fragile X premutation (Coffey et al., 2008). It is not yet known whether autoimmune disorders are increased specifically in women with FXPOI.

Prediction of risk for FXPOI

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) (Allen et al., 2007; Ennis et al., 2006; Mailick et al., 2014; Spath et al., 2011b; Sullivan et al., 2005). One study estimated the risk of FXPOI to be 38% in this high risk group (Allen et al., 2007), although more studies are needed to better define high risk alleles and the reason for this non-linear association. Irrespective, all premutation carriers have at least a small increased risk above that found in the general population (Spath et al., 2011b). Smoking is another known risk factor that decreases age at menopause. This is true for all women, not just women who carry the premutation (Allen et al., 2007). Lastly, data suggest that other

genes may modify the age of onset for FXPOI, those that may or may not interact directly with FMR1 (Allen et al., 2014; Hunter et al., 2008; Spath et al., 2011b). More work is being done to identify these genes.

Diagnosis

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. Reduced levels of anti-Mullerian 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 (Rohr et al., 2008; Spath et al., 2011a). 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. Initial investigations should include a pregnancy test, measurement of serum FSH, prolactin, and thyroid hormone levels to assess for other medical conditions, such as thyroid disease, polycystic ovarian syndrome, or pregnancy, which can present similarly. 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.

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 clinical and emotional consequences associated with ovarian insufficiency. 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 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. Health care 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 is suggested.

2. 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 (Board of the International Menopause et al., 2007; Practice Committee of the American Society for Reproductive 2004). 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(Hipp et al., 2016). Thus, there needs to be increased awareness of the benefits of HRT for women with FXPOI. As noted by others (Gatta et al., 2015; Groff et al., 2005), the conclusions of the Women's Health Initiative (Rossouw et al., 2002) 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 by The North American Menopause Society until the median age of natural menopause (North American Menopause Society 2012).

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 (Mishell et al., 1971). The 100 micrograms (mcg) per day estradiol patch and vaginal ring deliver the appropriate amount of estradiol each day to maintain levels in the blood 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 (Canonico et al., 2007). 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. Cyclic medroxyprogesterone acetate 10 mg by mouth per day for 12 days per calendar month is highly recommended for protection against heavy menstrual bleeding, excessive growth of the lining of the uterus, and endometrial cancer.

Oral contraceptive pills are not indicated as a form of HRT in women with POI. Oral contraceptives exceed the amount of estrogen needed to maintain bone density. Also, oral contraceptives provide a continuous dose of estrogen and progestin (typically for three weeks followed by one week of placebo). It is more optimal to mimic the natural menstrual cycle with two weeks of estrogen exposure followed by two weeks of estrogen and progesterone combined ("physiologic HRT"). Of note, a study evaluating HRT regimens in rats with removed ovaries had improved bone mineral density when estrogen and progestin were not administered continuously, as they are in oral contraceptive pills

(Vanin et al., 1995). Furthermore, evidence has shown that oral contraceptive pills are not as effective at improving or maintaining bone density. Fifty-nine women with spontaneous POI were followed in a two-year open randomized trial comparing physiologic HRT to oral contraceptive pills and to no treatment. The study found that women taking physiologic HRT had significantly increased lumbar spine bone mineral density compared with women with POI taking oral contraceptive pills, but that both treatments were significantly better than no treatment (Cartwright et al., 2016). Also, a prospective three-year NIH 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 (Popat et al., 2014). 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. The fact that the women with POI were able to attain normal bone density is quite striking because normally in women, peak bone mass is not reached until the early 30s. 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, Hipp et al.(2016) 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 1000mg per day for women 19-50 years old and 1300mg 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 (Holick 2007). Calcium supplements increase bone mineral density, but may 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 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 (Nelson 2009). As mentioned above, on the appropriate regimen of physiologic HRT up to the typical age

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 (Alper et al., 1986). A menstrual diary is advised, with prompt pregnancy testing in the case of late menses.

5. Parenthood. There are several parenthood options available to women with FXPOI, depending the needs of the woman. 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. Some women may choose fertility treatment, such as in vitro fertilization (IVF), especially if looking to pursue preimplantation genetic diagnosis (PGD). However, fertility treatment with a woman's own eggs may not be successful given the severely diminished ovarian response, and some IVF centers may not offer IVF to women with FXPOI for this reason. 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.

In general, women diagnosed with POI who desire pregnancy should not take the oral contraceptive pill because it is known to create hostile cervical mucus, which impedes the ability of sperm to reach the egg should they ovulate. Also, the oral contraceptive pill is known to cause thinning in the lining of the uterus, which may impede implantation of the embryo should an egg be fertilized. 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. As noted previously, for women with POI, there is a 5-10% chance of spontaneous pregnancy (Taylor et al., 1996; van Kasteren et al., 1999). This rate may be higher (about 13%) as indicated in a recent study (Hipp et al., 2016). When a woman is diagnosed with FXPOI, a referral to a genetic counselor is very helpful 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.

Since mature oocyte cryopreservation is no longer considered experimental by the American Society for Reproductive, women at risk for POI may undergo fertility preservation. 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

National Fragile X Foundation: fxpoi.fragilex.org

Women's Health and the Premutation:

https://d3ojjekythoefp.cloudfront.net//wp-content/uploads/2012/01/FX-Premutation-Emory-12.13.15.pdf

https://fragilex.org.au/womens-health-and-the-fragile-x-premutation/

American Society for Reproductive Medicine: ReproductiveFacts.org (specifically for a fact sheet on POI: http://www.reproductivefacts.org/news-and-publications/patient-fact-sheets-and-booklets/fact-sheets-and-info-booklets/what-is-premature-ovarian-insufficiency-also-called-premature-ovarian-failure/)

References

Acog. (2010). ACOG Committee Opinion No. 469: Carrier screening for fragile X syndrome. Obstet Gynecol 116(4):1008-10.

Allen, E. G., Grus, W. E., Narayan, S., Espinel, W., Sherman, S. L. (2014). Approaches to identify genetic variants that influence the risk for onset of fragile X-associated primary ovarian insufficiency (FXPOI): a preliminary study. Front Genet 5:260.

Allen, E. G., Sullivan, A. K., Marcus, M., Small, C., Dominguez, C., Epstein, M. P., Charen, K., He, W., Taylor, K., Sherman, S. L. (2007). Examination of reproductive aging milestones among women who carry the FMR1 premutation. Human reproduction 22:2142-2152.

Alper, M. M., Jolly, E. E., Garner, P. R. (1986). Pregnancies after premature ovarian failure. Obstet Gynecol 67(3 Suppl):59S-62S.

Board of the International Menopause, S., Pines, A., Sturdee, D. W., Birkhauser, M. H., Schneider, H. P., Gambacciani, M., Panay, N. (2007). IMS updated recommendations on postmenopausal hormone therapy. Climacteric 10(3):181-94.

Bolland, M. J., Avenell, A., Baron, J. A., Grey, A., Maclennan, G. S., Gamble, G. D., Reid, I. R. (2010). Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ 341:c3691.

Canonico, M., Oger, E., Plu-Bureau, G., Conard, J., Meyer, G., Levesque, H., Trillot, N., Barrellier, M. T., Wahl, D., Emmerich, J., Scarabin, P. Y., Estrogen, Thromboembolism Risk Study, G. (2007). Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. Circulation 115(7):840-5.

Cartwright, B., Robinson, J., Seed, P. T., Fogelman, I., Rymer, J. (2016). Hormone Replacement Therapy Versus the Combined Oral Contraceptive Pill in Premature Ovarian Failure: A Randomized Controlled Trial of the Effects on Bone Mineral Density. J Clin Endocrinol Metab 101(9):3497-505.

Coffey, S. M., Cook, K., Tartaglia, N., Tassone, F., Nguyen, D. V., Pan, R., Bronsky, H. E., Yuhas, J., Borodyanskaya, M., Grigsby, J., Doerflinger, M., Hagerman, P. J., Hagerman, R. J. (2008). Expanded clinical phenotype of women with the FMR1 premutation. Am J Med Genet A 146(8):1009-1016.

De Caro, J. J., Dominguez, C., Sherman, S. L. (2008). Reproductive Health of Adolescent Girls Who Carry the FMR1 Premutation: Expected Phenotype Based on Current Knowledge of Fragile X-Associated Primary Ovarian Insufficiency. Ann N Y Acad Sci 1135:99-111.

Ennis, S., Ward, D., Murray, A. (2006). Nonlinear association between CGG repeat number and age of menopause in FMR1 premutation carriers. EurJ Hum Genet 14(2):253-255.

Gatta, L. A., Jiang, X., Schnatz, P. F. (2015). Hormone therapy in women with primary ovarian insufficiency or early menopause. Menopause 22(9):923-5.

Groff, A. A., Covington, S. N., Halverson, L. R., Fitzgerald, O. R., Vanderhoof, V., Calis, K., Nelson, L. M. (2005). Assessing the emotional needs of women with spontaneous premature ovarian failure. FertilSteril 83(6):1734-1741.

Hipp, H. S., Charen, K. H., Spencer, J. B., Allen, E. G., Sherman, S. L. (2016). Reproductive and gynecologic care of women with fragile X primary ovarian insufficiency (FXPOI). Menopause 23(9):993-9.

Holick, M. F. (2007). Optimal vitamin D status for the prevention and treatment of osteoporosis. Drugs Aging 24(12):1017-29.

Hunter, J. E., Epstein, M. P., Tinker, S. W., Charen, K. H., Sherman, S. L. (2008). Fragile X-associated primary ovarian insufficiency: evidence for additional genetic contributions to severity. Genet Epidemiol 32(6):553-559.

Mailick, M. R., Hong, J., Greenberg, J., Smith, L., Sherman, S. (2014). Curvilinear association of CGG repeats and age at menopause in women with FMR1 premutation expansions. Am J Med Genet B Neuropsychiatr Genet 165B(8):705-11.

Mishell, D. R., Jr., Nakamura, R. M., Crosignani, P. G., Stone, S., Kharma, K., Nagata, Y., Thorneycroft, I. H. (1971). Serum gonadotropin and steroid patterns during the normal menstrual cycle. Am J Obstet Gynecol 111(1):60-5.

Nelson, L. M. (2009). Clinical practice. Primary ovarian insufficiency. N Engl J Med 360(6):606-14.

North American Menopause Society. (2012). The 2012 hormone therapy position statement of: The North American Menopause Society. Menopause 19(3):257-71.

Popat, V. B., Calis, K. A., Kalantaridou, S. N., Vanderhoof, V. H., Koziol, D., Troendle, J. F., Reynolds, J. C., Nelson, L. M. (2014). Bone mineral density in young women with primary ovarian insufficiency: results of a three-year randomized controlled trial of physiological transdermal estradiol and testosterone replacement. J Clin Endocrinol Metab 99(9):3418-26.

Practice Committee of the American Society for Reproductive, M. (2004). Current evaluation of amenorrhea. Fertil Steril 82 Suppl 1:S33-9.

Rebar, R. W. (2009). Premature ovarian failure. Obstet Gynecol 113(6):1355-1363.

Rohr, J., Allen, E. G., Charen, K., Giles, J., He, W., Dominguez, C., Sherman, S. L. (2008). Anti-Mullerian hormone indicates early ovarian decline in fragile X mental retardation (FMR1) premutation carriers: a preliminary study. Hum Reprod 23(5):1220-1225.

Rossouw, J. E., Anderson, G. L., Prentice, R. L., Lacroix, A. Z., Kooperberg, C., Stefanick, M. L., Jackson, R. D., Beresford, S. A., Howard, B. V., Johnson, K. C., Kotchen, J. M., Ockene, J., Writing Group for the Women's Health Initiative, I. (2002). Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 288(3):321-33.

Sherman, S. L. (2000). Seminars in Genetics: Premature ovarian failure in the fragile X syndrome. American Journal of Medical Genetics 97 189-195.

Spath, M. A., Feuth, T. B., Allen, E. G., Smits, A. P., Yntema, H. G., Van Kessel, A. G., Braat, D. D., Sherman, S. L., Thomas, C. M. (2011a). Intra-individual stability over time of standardized anti-Mullerian hormone in FMR1 premutation carriers. Human reproduction (Oxford, England) 26(8):2185-91.

Spath, M. A., Feuth, T. B., Smits, A. P., Yntema, H. G., Braat, D. D., Thomas, C. M., Van Kessel, A. G., Sherman, S. L., Allen, E. G. (2011b). Predictors and risk model development for menopausal age in fragile X premutation carriers. Genetics in medicine : official journal of the American College of Medical Genetics 13(7):643-50.

Sullivan, A. K., Marcus, M., Epstein, M. P., Allen, E. G., Anido, A. E., Paquin, J. J., Yadav-Shah, M., Sherman, S. L. (2005). Association of FMR1 repeat size with ovarian dysfunction. Hum Reprod 20(2):402-412.

Taylor, A. E., Adams, J. M., Mulder, J. E., Martin, K. A., Sluss, P. M., Crowley, W. F., Jr. (1996). A randomized, controlled trial of estradiol replacement therapy in women with hypergonadotropic amenorrhea. J Clin Endocrinol Metab 81(10):3615-21.

Van Kasteren, Y. M., Schoemaker, J. (1999). Premature ovarian failure: a systematic review on therapeutic interventions to restore ovarian function and achieve pregnancy. Hum Reprod Update 5(5):483-92.

Vanin, C. M., Maclusky, N. J., Grynpas, M. D., Casper, R. F. (1995). The effect of three hormone replacement regimens on bone density in the aged ovariectomized rat. Fertil Steril 63(3):643-51.

Wheeler, A. C., Bailey, D. B., Jr., Berry-Kravis, E., Greenberg, J., Losh, M., Mailick, M., Mila, M., Olichney, J. M., Rodriguez-Revenga, L., Sherman, S., Smith, L., Summers, S., Yang, J. C., Hagerman, R. (2014). Associated features in females with an FMR1 premutation. Journal of neurodevelopmental disorders 6(1):30.

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*The **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. (800-688-8765 or fragilex.org)*