AUSTRALASIAN MENOPAUSE SOCIETY
EMPOWERING MENOPAUSAL WOMEN

Information Sheet

Fragile X and Premature Ovarian Insufficiency

KEY POINTS

- Fragile X disorders are due to the expansion of CGG repeats in the FMR1 gene on the X chromosome.
- The fragile X premutation (55-200 CGG repeats) affects 1/150-300 women
- 16-30% of premutation carriers will develop premature ovarian insufficiency (POI). The highest risk and earliest onset of POI is seen in women with 70-100 CGG repeats.
- There is an overlap between symptoms associated with fragile X premutation and POI
- Fragile X screening is recommended for all women diagnosed with spontaneous POI
- Management of fragile X POI is similar to other causes of POI
- Women with the fragile X premutation should be referred for genetic counselling and fragile X screening offered to family members. Referral for fertility preservation should be considered for premutation carriers

Definitions and Epidemiology

Fragile X disorders are due to the expansion of CGG repeats in the FMR1 gene on the X chromosome (Table 1). Healthy individuals have fewer than 44 repeats whereas the full mutation has >200 repeats, fragile X syndrome (FXS). FXS is a severe neurodevelopmental condition and the most common cause of inherited intellectual disability and autism in males[1]. Fragile X premutation (50-200 repeats) is associated with 3 conditions including: (i) **fragile X associated premature ovarian insufficiency (FXPOI)** where POI is defined as loss of ovarian function occurring in women younger than 40 years of age **[2];** (ii) fragile X associated tremor/ataxia syndrome (FX-TAS), and (iii) Fragile X associated neuropsychiatric disorder[1,3]. FX-TAS affects 16-18% of older female premutation carriers and FXS is seen in 25% of females, compared to 40% and 85% of males respectively[4,5]

The fragile X premutation occurs in 1/150-300 women[4,5] .The FMRI premutation is the most common monogenic cause of POI and FXPOI occurs in 16-30% of premutation carriers[5]. The risk of FXPOI varies with the number of repeats with the highest risk and earliest onset of POI seen in women with 70-100 CGG repeats, especially 85-89 repeats[5]. Other factors associated with an increased risk of FXPOI in premutation carriers include smoking, family history of POI/ early menopause and short menstrual cycles[5].

The pathophysiology underlying FXPOI is unclear but increased follicle atresia secondary to toxic mRNA accumulation and /or abnormal proteins has been proposed[3]. In addition,

intracellular calcium dysregulation, oxidative stress, mitochondrial abnormalities and DNA repair damage affecting neurons in FX-TAS has been reported but the role in ovarian dysfunction is unclear[1].

Table 1: Disorders associated with FMR1 gene mutation[1,3]

	Normal	Grey zone	Premutation	Full mutation
FMR1 Gene CCG repeats	<44	45-54	55-200	>200
mRNA			Increased	Absent
Protein			Abnormal and reduced levels	Absent
Phenotype	Healthy	Healthy but at risk of disease phenotypes	FX-POI FX-TAS FX-AND	Fragile X syndrome
FXPOI: Fragile X associated premature ovarian insufficiency; FX-TAS: Fragile X associated tremor/ataxia syndrome; FX-AND: Fragile X associated neuropsychiatric disorder				

Diagnosis

- POI should be considered in any woman presenting with oligo/amenorrhea or infertility, especially in women who are known premutation carriers. Diagnosis is often delayed as the woman or her doctor do not consider the possibility of menopause/POI as a cause of her symptoms. Evaluation of symptoms and exclusion of secondary causes of amenorrhea is necessary. Diagnostic criteria include FSH levels> 25 on 2 occasions at least 1 month apart following 4-6 months of amenorrhea (where the women is not receiving any hormone therapy)[2,11].
- A blood test for fragile X premutation should be performed in any woman diagnosed with spontaneous POI.
- Diagnosis can be stressful and difficult decisions may need to be made. A woman should be comfortable with her doctor as several consultations may be needed to establish the best management of this condition and plan for the future.
- Women should be referred for genetic counselling and fragile X screening should be offered to family members. Fertility preservation may be an option for affected premutation carriers who have not yet developed POI.
- There is no method to accurately predict who will develop POI currently.

What are the consequences?

- Loss of fertility, which for many women can be devastating.
- Oligo/amenorrhea may be the first indicator of early ovarian insufficiency.

- Symptoms of estrogen deficiency. These include hot flushes, mood change, sleep disturbance, vaginal dryness or poor lubrication during sexual arousal. These symptoms may occur even while the woman is still having menstrual periods. Symptoms may be more severe in comparison to women experiencing natural menopause[4]
- Psychological distress. Depression and anxiety are commonly experienced by women with POI. Women with the fragile X premutation overall have an increased risk of anxiety and depression[12]. However, FXPOI is associated with an earlier onset of anxiety and caring for a child with FXS increases the risk of anxiety and depression[12]. Women with POI often feel confused, sad, jealous of other women's pregnancies or old before their time. Psychological counseling can ease this distress. Use of menopausal hormone therapy (MHT), may help mood. Support from the woman's partner, family and friends is important. SSRI anti-depressants have been shown to be helpful with anxiety and depression in other fragile X associated disorders and may be helpful in this setting[1].
- Fragile X premutation carriers report a variety of symptoms including sleep problems, headaches, fibromyalgia, and autoimmune thyroid problems which may overlap with symptoms of POI [12] .
- Information regarding the long-term consequences of POI is derived from observational cohort studies with mixed causes of POI. These studies indicate a 2-3-fold increased risk of osteoporosis[13,14], increased risk of type 2 diabetes mellitus[15], and a 50% greater risk of cardiovascular disease[5,16,17]. Breast cancer risk may be reduced slightly[18]. There may also be an increased risk of cognitive problems, dementia and Parkinson's disease[19]. Greater risk is associated with younger age of menopause. Taking MHT until 45-50 years may minimize these long-term risks[2]. Osteoporosis has been observed in association with FXPOI specifically[12]

Fertility issues:

- Women with FXPOI have a 12 % chance of spontaneous pregnancy so if a woman does not want a pregnancy she should use contraception even if diagnosed with POI.
- Donor egg or embryo is the most effective method of achieving a pregnancy.
- Fertility preservation in premutation carriers without FXPOI may be an option using cryopreservation of oocytes or ovarian tissue. Pre-implantation genetic testing should be considered due to the potential for expansion of the CGG repeats in the offspring from the premutation to the full mutation and thus risk of FXS. CRISPR gene editing technology may offer the option to delete the expanded repeats in affected embryos in the future[4] .
- Some women choose not to become a parent, others may want to adopt or foster children.

Hormone Replacement Therapy:

- Compared with post-menopausal women aged over 50 years MHT in women with POI can be considered as "hormone replacement therapy" (HRT) as the hormone therapy in this instance is replacing the hormones which the ovaries would otherwise be producing.
- Unless contra-indicated (for example oestrogen sensitive cancer), women with POI are advised to take MHT to relieve the symptoms of oestrogen deficiency and prevent long term complications. Higher oestrogen doses may be required compared with older women for symptom relief and for bone protection. Current recommendations are to continue MHT until the age of average menopause at approximately 51 years[6, 7].
- Options include oestrogen tablets, patches, or gels. Oestrogen alone therapy is used in women who have had a hysterectomy (see AMS information sheet: Oestrogen Only Menopausal Hormone Therapy). Oestrogen combined with a progestogen is required if a women has not had a hysterectomy (see AMS information sheets: Combined Menopausal Hormone Therapy and Oestrogen Only Menopausal Hormone Therapy). In addition, regular vaginal oestrogen can be used to improve dyspareunia.
- The combined oral contraceptive pill (OCP) can be used as a replacement hormone up to the age of 50 if the woman has no contraindications to its use including risk factors or a personal history of venous blood clots, hypertension or is a current smoker and older than 34 years. Continuous or extended cycle use of the OCP is preferred as women may experience a return of symptoms when the inactive tablets are taken and to optimize bone health[20].
- Testosterone therapy has been shown to helpful for postmenopausal women with reduced libido but data is lacking for women with POI. (See AMS information sheet: Sexual Difficulties in the Menopause).

Prevention of bone loss:

- Osteoporosis is common in women who have had oestrogen deficiency from a young age. It is important to check bone mineral density at diagnosis and every two years, particularly if the woman decides against taking MHT as use of MHT prevents bone loss.
- A healthy lifestyle is important to maintain bone health. Women with POI should avoid smoking, engage in regular weight-bearing exercise, and ensure adequate dietary intake of calcium and vitamin D.
- If a woman suffers a bone fracture from osteoporosis, there are several proven therapies available to reduce her risk of further fractures. However, specialist consultation may be required to consider future fertility requirements and impact of anti-resporptive therapy.

Prevention of cardiovascular disease:

- POI is associated with an increased risk of cardiovascular disease (CVD). Some studies suggest that this risk is minimized in women who take MHT.
- Women with POI should minimize CVD risk by maintaining normal weight, exercising regularly, ceasing smoking, maintaining a healthy diet, controlling diabetes mellitus and high blood pressure, and preventing or treating high levels of cholesterol and triglycerides.

Further information:

- Fragile X Association of Australia: https://www.fragilex.org.au
- Fragile X New Zealand: https://fragilex.org.nz/
- Early Menopause: Experiences and Perspectives of Women and Health Practitioners: https://healthtalkaustralia.org/early-menopause-experiences-and-perspectives-of-women-and-health-professionals/
- The Jean Hailes Foundation: www.jeanhailes.org.au
- ACCESS: Australia's National Infertility Network www.access.org.au
- NZ Early Menopause Support www.earlymenopause.org.nz
- The Daisy Network Premature Menopause Support Group: www.daisynetwork.org.uk
- Fertility NZ, the NZ national fertility support network: www.fertilitynz.org.nz

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References

1. Hagerman RJ, Protic D, Rajaratnam A, Salcedo-Arellano MJ, Aydin EY, Schneider A. Fragile X-Associated Neuropsychiatric Disorders (FXAND). *Front Psychiatry* 2018; **9**: 564.
2. Webber L, Davies M, Anderson R, et al. ESHRE Guideline: management of women with premature ovarian insufficiency. *Hum Reprod* 2016; **31**(5): 926-37.
3. Rosario R, Anderson R. The molecular mechanisms that underlie fragile X-associated premature ovarian insufficiency: is it RNA or protein based? *Molecular Human Reproduction* 2020; **26**(10): 727-37.
4. Fink DA, Nelson LM, Pyeritz R, et al. Fragile X Associated Primary Ovarian Insufficiency (FXPOI): Case Report and Literature Review. *Frontiers in genetics* 2018; **9**.
5. Allen EG, Charen K, Hipp HS, et al. Refining the risk for fragile X-associated primary ovarian insufficiency (FXPOI) by FMR1 CGG repeat size. *Genet Med* 2021; **23**(9): 1648-55.
6. Golezar S, Ramezani Tehrani F, Khazaei S, Ebadi A, Keshavarz Z. The global prevalence of primary ovarian insufficiency and early menopause: a meta-analysis. *Climacteric* 2019; **22**(4): 403-11.
7. Chemaitilly W, Li Z, Krasin MJ, et al. Premature Ovarian Insufficiency in Childhood Cancer Survivors: A Report From the St. Jude Lifetime Cohort. *The Journal of Clinical Endocrinology & Metabolism* 2017; **102**(7): 2242-50.
8. Mishra GD, Chung H-F, Cano A, et al. EMAS position statement: Predictors of premature and early natural menopause. *Maturitas* 2019; **123**: 82-8.
9. Davis S, Lambrinoudaki I, Lumsden MA, et al. Menopause. *Nature Reviews Disease Primers* 2015; **1**: 1-19.

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10. Laven JS. Genetics of Early and Normal Menopause. *Seminars in Reproductive Medicine* 2015; **33**(6): 377-83.
11. Yeganeh L, Boyle JA, Wood A, Teede H, Vincent AJ. Menopause guideline appraisal and algorithm development for premature ovarian insufficiency. *Maturitas* 2019; **130**: 21-31.
12. Allen EG, Charen K, Hipp HS, et al. Clustering of comorbid conditions among women who carry an FMR1 premutation. *Genet Med* 2020; **22**(4): 758-66.
13. Xu X, Jones M, Mishra GD. Age at natural menopause and development of chronic conditions and multimorbidity: results from an Australian prospective cohort. *Human Reproduction* 2020; **35**(1): 203-11.
14. Anagnostis P, Siolos P, Gkekas NK, et al. Association between age at menopause and fracture risk: a systematic review and meta-analysis. *Endocrine* 2019; **63**(2): 213-24.
15. Anagnostis P, Christou K, Artzouchaltzi AM, et al. Early menopause and premature ovarian insufficiency are associated with increased risk of type 2 diabetes: a systematic review and meta-analysis. *European Journal of Endocrinology* 2019; **180**(1): 41-50.
16. Zhu D, Chung HF, Dobson AJ, et al. Age at natural menopause and risk of incident cardiovascular disease: a pooled analysis of individual patient data. *Lancet Public Health* 2019; **4**(11): e553-e64.
17. Muka T, Oliver-Williams C, Kunutsor S, et al. Association of Age at Onset of Menopause and Time Since Onset of Menopause With Cardiovascular Outcomes, Intermediate Vascular Traits, and All-Cause Mortality: A Systematic Review and Meta-analysis. *JAMA Cardiology* 2016; **1**(7): 767-76.
18. Collaborative Group on Hormonal Factors in Breast C. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. *Lancet Oncol* 2012; **13**(11): 1141-51.
19. Faubion SS, Kuhle CL, Shuster LT, Rocca WA. Long-term health consequences of premature or early menopause and considerations for management. *Climacteric* 2015; **18**(4): 483-91.
20. Gazarra LBC, Bonacordi CL, Yela DA, Benetti-Pinto CL. Bone mass in women with premature ovarian insufficiency: a comparative study between hormone therapy and combined oral contraceptives. *Menopause* 2020.