Clinician's guide

Fragile X-Associated Primary Ovarian Insufficiency(FXPOI)

What is FXPOI?

FXPOI is a condition caused by a premutation (55-200 CGG repeats) in the *FMR1* gene. As a result, females experience irregular or cessation of menses before age 40. Females with a premutation have a 20% (1/5) risk of FXPOI, with the **highest** risk of FXPOI being **80-100** repeats.

Statistics

- ~1 in 151 females carry a *FMR1* premutation, impacting over 1 million women in the U.S.
- FXPOI affects 1 in 5 women with a premutation

Study on FXPOI diagnostic odyssey

Patient resource

Signs and Symptoms

- Irregular menstrual cycling, ~4-6 months, or cessation of menses before 40 y/o
- Menopause symptoms (e.g. vaginal dryness, night sweats, hot flashes)
- Altered hormone profile
  - Increased FSH: >30-40 mIU/mL
  - Decreased estradiol: < 50 pg/mL
- Infertility
- Family history: early menopause, intellectual disability, infertility, tremor/ataxia

Management Guidelines

1 Screening

- FSH, estradiol, and AMH evaluation for women with unexplained POI symptoms
- Offer fragile X premutation carrier screening for women with:
  - A personal or family history of ovarian failure or an elevated FSH level <40 y/o without a known cause
  - A family history of fragile X-related disorders or intellectual disability suggestive of fragile X syndrome
- Carrier screening should be offered to all patients considering or planning pregnancy

2 Management

- Genetic counseling to discuss the premutation, FXPOI, personal and reproductive risk, and inheritance
- Referral to a REI to discuss hormone replacement therapy (HRT), thyroid screening, and bone density assessment
- Education on all reproductive options
- Point of care provider established with an OBGYN or REI
- Connections to patient groups, support networks, and mental health resources

3 Long Term Care

- Monitored care provided by clinicians for symptoms and comorbidities
- REI visit every 1-2 years for HRT and TSH evaluation

Reproductive Risks

- Risk for a premutation expansion to a full mutation in offspring increases with the number of CGG repeats
- AGG interruptions can reduce the risk of expansion to a full mutation
- Reproductive counseling:
  - in vitro fertilization with pre-implantation genetic testing
  - egg donation or adoption
  - prenatal diagnostic testing

Comorbidity Risks

***FMR1* Premutation and/or FXPOI**

- Osteoporosis
- Anxiety, depression
- Hypothyroidism
- Migraines, tension headaches
- Cardiovascular disease

ACOG committee opinion #605 &691; Hipp, H. S., et al., doi: 10.1097; Poteet, B., et al., doi: 10.1007