Before, Between & Beyond Pregnancy
The National Preconception Curriculum and Resources Guide for Clinicians

Guidance for Preconception Fragile X Carrier Screening

Colleen Landy Schmitt. MS, CGC
Genetic Counselor
Department of Obstetrics & Gynecology
University of North Carolina at Chapel Hill

This guidance should not substitute for clinical judgments or expert consultation

Fragile X Carrier Screening Care and Counseling Guidelines:

- Fragile X syndrome is the most common inherited cause of mental retardation and the most common single gene mutation associated with autism. It is caused by an expansion of CGG repeats in the FMR1 gene, which is located on the X chromosome.
- The number of CGG repeats is associated with different phenotypes, including classic fragile X syndrome, premature ovarian failure (POF) and fragile X associated tremor/ataxia syndrome (FXTAS).

Table 1: FMR1 Expansion

	CGG Repeat Length	Phenotype	Prevalence
Normal	12-44	-	-
Intermediate/Grey Zone	45-54	None	1/72-1/145
Premutation	55-200	POF (females) FXTAS (males)	1/250 (females) 1/800 (males)
Full mutation	200+	Carrier/Mild Fragile X Syndrome (females) Fragile X Syndrome (males)	1/303 (females) 1/4000 (males)

- Larger CGG repeats are unstable and often expand when passed from mother to offspring. Intermediate alleles may expand to a premutation, but have not been shown to expand to a full mutation in a single generation. Premutation alleles are at significant risk of expansion to a full mutation in a subsequent generation. Therefore:

        - ❖ Women with an intermediate allele may have children at risk for POF and FXTAS, but would not be expected to have a child with fragile X syndrome.
        - ❖ Women with a premutation are at risk to have a child with fragile X syndrome, as well as to develop POF. The prevalence of FXTAS in women is low.
    - o Fragile X testing is recommended for patients presenting with mental retardation, evidence of ovarian failure before 40 years of age and neurological findings including non-resting tremor, ataxia, and autonomic dysfunction after 50 years of age.
    - o Fragile X carrier screening should be offered to patients who are pregnant or contemplating pregnancy if there is a family history of mental retardation or findings suggestive of POF or FXTAS.
    - o General population screening for fragile X syndrome is not recommended at this time, though individual centers may choose to offer it to preconception patients.
    - o Genetic counseling is recommended after identification of intermediate alleles, premutation alleles and full mutations, regardless of how they are ascertained.
    - o While preconception is the ideal time to proceed with fragile X carrier screening, it may not be covered by all insurance plans. As with any genetic test, it is recommended patients confirm coverage of testing with their individual insurer before proceeding.