

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

**Guidance for Preconception Fragile X
Carrier Screening**

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This guidance should not substitute for clinical judgments or expert consultation

Prenatal Screening and Diagnosis of Fragile X Syndrome

Cronister A, Teicher J, Rohlfs EM, Donnenfeld A, Hallam S. Prevalence and instability of fragile X alleles: Implications for offering fragile X prenatal diagnosis. Am J Obstet Gynecol 2008;111(3):596-601.

Fragile X syndrome is the most common inherited cause of mental retardation, found in approximately 1/4000 males and 1/8000 females. Inherited in an X-linked manner, it has been estimated that approximately 1/303 females with no reported family history of the disorder are carriers for a disease causing mutation. This prevalence appears to be consistent among most racial and ethnic groups.

Fragile X syndrome has been linked to an unstable CGG trinucleotide sequence located in the 5' untranslated region of the FMR1 gene. Typical alleles range from 6 to 44 repeats. Alleles with 45-54 repeats are considered intermediate or "gray zone" alleles and have not been observed to display expansion to a full mutation in one generation. Premutation alleles, defined as 55-200 repeats, are generally unstable and may result in an expansion to a full mutation, or greater than 200 repeats, when passed from mother to child.

Current carrier screening guidelines include offering testing to patients with a family history of mental retardation, fragile X syndrome, and suspected or known carriers of the fragile X premutation or full mutation, as well as any woman who has ovarian failure or an elevated follicle stimulating hormone level before 40 years of age without a known cause. An increasing number of centers are also offering fragile X carrier screening routinely to all prenatal patients.

The current study aimed to determine the frequency of FMR1 intermediate alleles, premutations and full mutations in four populations, including individuals with (1) a family history of fragile X syndrome, (2) a family history of mental retardation, (3) a

personal history of premature ovarian failure and (4) no family history suggestive of fragile X syndrome. They also examined the expansion of the fragile X CGG repeat when passed from mothers to offspring.

DNA testing was completed for 14,675 women referred for fragile X carrier testing. Overall, 1 in 71 women were found to have a premutation or full mutation in the FMR1 gene. Prevalence was highest in women with a known family history of fragile X syndrome, with 1 in 4 women having a premutation and 1 in 15 with a full mutation, and in women with a history of premature ovarian failure, with 1 in 10 women being identified as a premutation carrier. Among women with a suspicious family history, 1/86 were found to carry a full or premutation, and 1/257 women with no family history were found to carry a premutation.

Ninety-three point four percent (93.4%) of intermediate alleles remained stable through transmission from mother to child. Of the 6.6% that expanded, two expanded to a premutation (55-200 repeats) and none expanded to a full mutation (>200 repeats). Seventy three point one percent (73.1%) of premutation alleles exhibited expansion in the next generation. Of these, 10 remained in the premutation range and 39 expanded to a full mutation. The smallest premutation to expand to a full mutation was 60 repeats. All mutations of greater than 85 repeats expanded to a full mutation upon transmission from mother to child.

Results of this study support current guidelines, which recommend fragile X carrier screening in women with a family history of fragile X syndrome and mental retardation, and with a personal history of premature ovarian failure. Due to the frequency (1/257) of an FMR1 premutation noted in the patients without a relevant family or personal history, the authors also suggest fragile X screening for all prenatal patients would be of benefit.

If a result in the intermediate range (45-54 repeats) is identified, the authors suggest that providers stress the result is of no immediate clinical significance, as mutations with fewer than 55 repeats have not been shown to expand to a full mutation in a single generation. Therefore, there is little risk of classic fragile X syndrome in offspring. The authors recommend offering prenatal diagnosis to patients with an identified full or premutation in the FMR1 gene, but state that prenatal diagnosis in individuals with an intermediate allele is of poor clinical utility.