Prenatal Screening for Fragile X: Carriers, Controversies, and Counseling

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In addition to causing developmental disability in future offspring, fragile X carrier status has important reproductive and mental health implications for the individual being tested. Accordingly, prenatal carrier screening and diagnosis using DNA-based molecular methods has become crucial in early detection, intervention, and family planning. Although the list of known genetic disorders is growing daily, controversy remains over who should be tested for fragile X. *FMR1* gene mutations can result in inherited intellectual disability, infertility, and neurodegeneration syndromes that are encountered by clinicians in a variety of settings. Patients and clinicians are still largely unfamiliar with this disorder, its complicated inheritance, and its heterogeneous phenotype. Debate continues over who should be offered prenatal carrier screening. As more disease screening is offered, pretest counseling will become only more complex and clinicians will further struggle to balance the needs of the individual and allocation of public health resources.

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KEY WORDS

Fragile X syndrome • *FMR1* gene mutation • Prenatal screening • Genetic counseling

Unlike most prenatal carrier testing, Fragile X carrier status has important reproductive and health implications both for the individual being tested as well as potential risks for developmental disability in future offspring. Clinicians in a variety of settings encounter the infertility, intellectual disability and neurodegenerative syndromes resulting from *FMR1* mutations. Accordingly, physicians must be comfortable with patient counseling regarding Fragile X and should remain vigilant in identifying patients who have indications for prenatal screening. Below we review the complicated inheritance of Fragile X and its varied phenotype. The current guidelines for prenatal screening are described and common counseling issues are addressed. Finally, we discuss universal prenatal carrier screening, a topic which will become only more complex as clinicians further struggle to balance the needs of the individual and allocation of public health resources.

Which of the Following Patients Should Be Offered Prenatal Carrier Screening for Fragile X?

Case 1

DM is a 33-year-old white woman who presents to your clinic during her first pregnancy for a first trimester screen for fetal aneuploidy. You take an extended history to determine her risk for a variety of genetic carrier screening tests available to her. She tells you that her maternal grandmother died of breast cancer at age 73. Her maternal grandfather lived to be age 75, but was severely demented toward the end of his life. DM's parents are living and healthy. Her older sister is healthy but has a son with mental retardation. Her younger brother is age 21 and healthy with no children.

Case 2

JP is a 32-year-old newlywed who comes to your clinic for preconception counseling. She is concerned that she may have some trouble getting pregnant as infertility seems to "run in her family." JP's older sister began to have hot flashes at age 34. Her older sister required in vitro fertilization to conceive her niece, who is healthy. Shortly after having her only daughter at age 37, her sister was told that she had gone through menopause. JP wants to know if there is any way to predict if she will have similar problems. The remainder of JP's family history is unremarkable for infertility or mental retardation.

Case 3

RG is a 42-year-old woman who presents to your reproductive endocrinology clinic with her partner for in vitro fertilization. She is a college biology professor and has read a lot about the process. An unrelated family friend has donated her eggs for the couple's use. RG would like to learn as much as possible about the pregnancy and asks you what genetic tests will be run on the donor eggs prior to implantation.

Fragile X Syndrome

Fragile X syndrome is the most common inherited form of intellectual and developmental disability worldwide. It has an estimated prevalence of 1 in 3600 males, and 1 in 4000 to 6000 females in various ethnic groups. Unlike other causes of mental retardation such as Down syndrome, phenotypic features of fragile X often are not apparent until later in childhood, making it difficult to diagnose during the newborn period. The mean age of diagnosis is age 3 years, and one study found that approximately one-quarter of families had a second child with the full mutation before the first child was diagnosed.[1] In addition to causing developmental disability in future offspring, fragile X carrier status has important reproductive and mental health implications for the individual being tested. Accordingly, prenatal carrier screening and diagnosis using DNA-based molecular methods has become crucial in early detection, intervention, and family planning. Although the list of known genetic disorders is growing daily, controversy remains over who should be tested for fragile X.

Genotype

The molecular genetics of fragile X syndrome are uniquely complex. Fragile X syndrome is an X-linked, dominant disorder caused by the expansion of an unstable cysteine-guanine-guanine (CGG) trinucleotide repeat on the 5′ untranslated region of the fragile X mental retardation-1 gene (*FMR1*). Mutations are categorized into four allelic forms based on repeat size: unaffected (< 45 repeats), intermediate (45-54 repeats), premutation (55-200 repeats), and full mutation (> 200 repeats).[2]

The large repeat length in the fragile X full mutation results in methylation and subsequent inactivation of the *FMR1* gene. This results in decreased encoding of the fragile X mental retardation protein, which may be important for protein synthesis regulation at the level of the dendritic spine.[3] Males with the full mutation all exhibit clinical features of fragile X syndrome. Females with the full mutation may or may not exhibit features of fragile X syndrome, depending on the degree of X inactivation. X inactivation is the random silencing of one of the X chromosomes in the cells of all female mammals. If the mutated chromosome is inactivated, its gene product is not produced and the resulting phenotype is less severe.

In addition, the inheritance pattern of fragile X is distinctive because unstable alleles may undergo mitotic expansion when transmitted from female carriers to offspring (Table 1). In this way, premutation carriers, who themselves display no cognitive impairment and may have no family history of cognitive impairment, may have offspring with the full mutation and therefore fragile X syndrome. The prevalence of premutation carriers in the United States is approximately 1 in 86 women with a family history of mental retardation and 1 in 257 women without

The prevalence of premutation carriers in the United States is approximately 1 in 86 women with a family history of mental retardation and 1 in 257 women without any known risk factors for fragile X syndrome.

TABLE 1

Maternal Allele Classification and Expansion to Full Mutation

Maternal Mutation Status	Maternal CGG Repeat Size	Full Mutation Expansion (%) in Next Generation
Unaffected	< 45	0
Intermediate	45-54	0
Premutation	55-59	< 2
	60-69	2
	70-79	32
	80-89	74
	90-99	94
	100-200	98
Full Mutation	> 200	

Data from Nolin SL et al.[33]

any known risk factors for fragile X syndrome.[4] Moreover, premutation carriers may also suffer from fragile X–associated premature ovarian insufficiency and tremor/ataxia syndrome. It is thought that in premutation carriers, FMR1 mRNA is produced in toxic amounts in leukocytes and neurons, resulting in these disorders.[5]

Intermediate mutations have not been shown to expand to a full mutation in one generation. Still, alleles of this size may be associated with fragile X syndrome in future generations or distant relatives.[6]

Phenotype

Males with the full fragile X mutation present with intellectual impairment ranging from learning disability to mental retardation, autism, and severe behavioral difficulties (Table 2). Males also display characteristic physical features, such as long, narrow faces, prominent ears, connective tissue laxity, muscle hypotonia, and macro-orchidism. The prevalence and severity of fragile X syndrome in females is attenuated because of X-inactivation. Still, approximately 50% of females with the fragile X full mutation will show some features of the disorder.

Fragile X is the most commonly identified cause of autism, a pervasive developmental disorder characterized by impaired social interaction, communication, and restricted, stereotyped behaviors. Studies estimate that 5% of patients with autism have fragile X.[7] Twenty-five percent of boys with fragile X and 6% of girls with fragile X meet the diagnostic criteria for autism.[8,9] In addition, the majority of patients with fragile X will display some autistic symptoms such as poor eye contact, hand flapping, and speech perseveration. Lower levels of fragile X mental retardation protein have been correlated with higher scores on neuropsychological measures of autism.[9] Current guidelines suggest that all children with autism be offered genetic counseling and testing for fragile X syndrome.[10] Some studies have proposed, however, that children with fragile X will demonstrate a unique profile of autism symptoms when compared with children with idiopathic autism.[11]

Women who are carriers of the fragile X premutation are not only at risk of transmitting the fragile X full mutation to their offspring, but are also at increased risk of developing primary ovarian insufficiency. Schwartz and colleagues conducted the first study to investigate the gynecologic histories of premutation and full mutation

TABLE 2

Clinical Features of FMR1-related Disorders

Fragile X syndrome	Large occipitofrontal head circumference Long face, prominent jaw, prominent ears Macroorchidism Connective tissue laxity, mitral valve prolapse Hypotonia Intellectual disability, low IQ, speech and motor delay Behavioral problems, autism and attention deficit spectrum disorders
Fragile X–associated premature ovarian insufficiency	Premature ovarian failure prior to age 40 Impaired ovarian response
Fragile X–associated tremor/ataxia syndrome	Intention tremor Cerebellar gait ataxia Dementia

carriers in 1994, showing that premutation carriers had higher rates of irregular menses and use of hormones to aid fertility than full mutation carriers and noncarriers.[12] The phrase fragile-X–associated premature ovarian insufficiency (FXPOI) encompasses the variety of ovarian dysfunction observed in premutation carriers. Approximately 20% of carriers with the fragile X premutation experience overt ovarian failure (absent menses and elevated follicle-stimulating hormone prior to age 40) compared with 1% of the general population. In addition, premutation carriers experience menopause, on average, 5 years earlier than the general population. Two percent of patients seen in fertility clinics with premature ovarian failure are found to have the fragile X premutation—much higher than rates in the general population.[13] Of note, recent research in fertility clinics has also shown an increased association between occult primary ovarian insufficiency (regular menses but impaired ovarian response) and the fragile X premutation.[14] Therefore, the fragile X premutation is likely to be an important cause of decreased fecundity that should be considered in reproductive endocrinology clinics.

Premutation carriers may also suffer from a neurodegenerative disorder known as fragile X–associated tremor/ataxia syndrome (FXTAS) later in life. Onset is typically in the sixth decade of life and is thought to affect approximately 40% of male premutation carriers and 80% of female carriers over age 50.[15] Currently, most patients with FXTAS are only identified after a grandchild is diagnosed with fragile X syndrome despite the fact that FXTAS is the most common known single-gene cause of tremor/ataxia in the elderly. This is likely because of decreased familiarity of many physicians with this disorder and the heterogeneity with which it presents. The presenting symptom is often an isolated intention tremor progressing to cerebellar gait ataxia, frontal executive dysfunction, and psychiatric derangements.[16] Magnetic resonance imaging in such patients displays global brain atrophy and white matter lesions of the middle cerebellar peduncles.[17] FXTAS is a progressive disorder with a life expectancy of 5 to 20 years from time of diagnosis. At the end stage, patients are often bedridden, demented, dysarthric, and incontinent.

Who Should Be Screened?

Current guidelines from the American Congress of Obstetricians and Gynecologists (ACOG) recommend prenatal screening and genetic counseling for fragile X in women with a family or personal history of fragile X, unexplained mental retardation or developmental delay, or premature ovarian insufficiency (Table 3).[18] In addition, ACOG recommends that all women who request fragile X carrier screening be offered DNA testing after appropriate genetic counseling.[18] The American College of Medical Genetics (ACMG) adds that DNA analysis for fragile X syndrome should be included as part of the diagnostic evaluation in patients with isolated cognitive impairment or cerebellar ataxia and intention tremors, especially if they are male.[10]

Is There a Role for Universal Prenatal Carrier Screening?

Prenatal carrier screening programs in women who do not have the above indications for testing have been debated for a variety of reasons. First, fragile X has clinically significant adverse consequences on affected individuals and their families comparable to Down syndrome.[19] The incidence of fragile X is similar to genetic diseases for which we already offer routine screening, such as cystic fibrosis.[20] Furthermore, adherence to current screening guidelines may only identify about 50% of fragile X carriers.[21] A recent survey has shown that a majority of genetic health professionals supported prenatal fragile X screening programs.[22]

Fragile X prenatal screening serves a dual purpose: it allows patients to make educated reproductive decisions and it gives them information about their personal

TABLE 3

Current ACOG and ACMG Guidelines

Who Should Be Offered Screening?	
Any patient with a personal or family history of...	• Fragile X or fragile X–related disorders • Unexplained mental retardation or developmental delay • Autism • Ovarian insufficiency or elevated FSH at age < 40 years of unknown cause
Men with....	• Isolated cerebellar ataxia with tremor • Isolated cognitive impairment
Any woman who requests fragile X carrier screening regardless of history	

ACMG, American College of Medical Genetics; ACOG, American Congress of Obstetricians and Gynecologists; FSH, follicle-stimulating hormone.

health. Accurate prenatal fetal diagnosis is available and the choice can be offered whether to continue pregnancy. Parents of children with fragile X have expressed the desire for prenatal screening because it would lead to earlier diagnosis, interventions, and altered family planning.[23,24] Similarly, identification of carriers at risk for premature ovarian failure may allow for earlier and more effective reproductive interventions in those desiring pregnancy. Finally, it has been shown that screening all women prenatally, regardless of family history or specific risk factors, is cost effective when considering the burden of raising a child with fragile X syndrome.[25,26]

Prenatal Diagnosis

Highly accurate prenatal diagnosis of fetuses at risk for fragile X is currently available via chorionic villus sampling (CVS) and amniocentesis. Expansion and methylation status of prenatal samples can be determined using a combination of polymerase chain reaction and southern analysis. Methylation results must be interpreted with caution from CVS and patients should be aware that a follow-up amniocentesis may be required if testing yields an ambiguous result. Information about gender acquired at the time of sampling can aid patients and clinicians in approximating phenotypic severity, with female fetuses typically having milder disease.

All pregnant women who are full mutation or premutation carriers should be offered prenatal diagnosis.[27] Recommendations for prenatal diagnosis for intermediate carriers are difficult to make and must be made on a case-by-case basis. On one hand, prenatal diagnosis gives information about allele instability and potential health risks for future offspring. For example, an intermediate carrier could discover that her daughter is a premutation carrier, prompting early discussion about reproductive choices when that daughter is older. Particularly anxious women may also find reassurance in fetal diagnosis, putting them at ease for the remainder of their pregnancy. On the other hand, prenatal diagnosis may cause undue angst in intermediate carriers when there is no demonstrated risk of expansion to the full mutation in one generation.

The identification of cell-free fetal DNA and RNA in maternal circulation holds promise for future development of noninvasive fragile X prenatal diagnosis. Cell-free fetal DNA testing is commercially available worldwide to determine gender, aneuploidy, and fetal RhD blood type.[28] Monogenic testing is in development.[29] Although cell-free fetal DNA is safe for the fetus, its cost and lower sensitivity and specificity have prevented it from replacing older techniques.[30]

Unique Challenges for Prenatal Genetic Counseling

Fragile X carrier testing raises distinctly complicated genetic counseling issues. First, an extensive multigenerational family history must be taken to assess whether screening would be beneficial to the patient. When physicians consider *FMR1* testing, this history must include developmental, neurodegenerative, and reproductive disability across multiple generations.[31] Patients are generally unaware of fragile X prior to counseling, and, as such, the complexity of the fragile X inheritance pattern may be overwhelming to them. Physicians and counselors must educate patients about the varied outcomes possible and the implications of detecting full allele, premutation allele, and intermediate allele carrier results. Ideally, women should have sufficient time to review and consider the information given to them about carrier testing and reflect on their own psychosocial situation prior to making a decision about testing.

Premutation carriers identified in the prenatal setting should be offered fetal diagnostic testing. New evidence suggests that the number of AGG interruptions may predict the risk of expansion of alleles with 45 to 69 repeats in the next generation.[32] Currently, however, it is very difficult to accurately estimate an individual's risk for *FMR1* intermediate and premutation allele expansion. Of note, it was observed that women who carry newly identified fragile X premutation alleles and have no family history of fragile X have dramatically lower expansion rates to full mutations than patients with a positive family history.[33] This result may be comforting to some patients. Women identified as carriers must be counseled about the risk for ovarian dysfunction and the reproductive options that are available to them. Family dynamics must also be considered and advice should be offered regarding testing other at-risk family members.

Intermediate carrier results may provoke worry because the risk for expansion, although very low, is uncertain. In addition, intermediate carriers should be notified that fragile X testing should be offered to future generations to determine allele stability and identify those at risk for offspring with the full mutation.

Prenatal identification of female fetuses with the fragile X full mutation also poses a significant challenge. X inactivation modifies the clinical phenotype in females so that the cognitive impairment is typically less severe than in males. Yet approximately 50% of females with the full mutation are affected,

and phenotypic severity cannot be predicted prenatally.[34] Uncertainty about the resulting phenotype generates significant anxiety and parents have a difficult choice to make.

Concerns regarding sufficient patient counseling and education are some of the greatest challenges to the implementation of widespread carrier screening. Still, existing prospective studies evaluating patient understanding and attitudes in such a screening program are limited in number, sample size, and diversity. A small, Internal Review Board–approved, pilot study was conducted at our institution with 100 women to ascertain their understanding of fragile X after genetic counseling and the motivations behind their prenatal screening choices. Seventy-two percent of the participants had never heard of fragile X prior to being counseled by the researcher. On a postcounseling quiz about fragile X syndrome and its inheritance pattern, 90% of the participants scored better than chance with a median score of 5 out of 6 true/false format questions answered correctly. Approximately 88% rated the counseling session as either helpful or extremely helpful. A total of 94% decided to undergo prenatal carrier screening for fragile X, with 54% selecting "I want to know" as their primary motivation.[35]

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Follow-up of Clinical Cases

It is hoped that while reading the three clinical vignettes at the beginning of this article, prenatal screening for fragile X came to mind. In Case 1, DM's nephew with mental retardation should prompt the clinician to investigate further and to ask whether a cause of the mental retardation was found. Unexplained mental retardation or developmental delay in a patient's family history is an indication for prenatal testing. In addition, the clinician should inquire further about the demented grandfather who may have had signs of FXTAS. In Case 2, JP has a sister with early onset menopause that may be suggestive of FXPOI. JP should be offered screening because carrier status may alter a woman's family-planning goals. JP may wish to preserve her fertility through methods such as oocyte cryopreservation or opt to have children earlier in life. Case 3 is more controversial as there are no clear indications for testing; however, failure to screen the donor eggs for fragile X could have grave consequences. RG did not inquire specifically about fragile X testing, but would like to know as much as possible about her potential pregnancy. Current ACOG guidelines do not recommend screening in such cases, but many providers would still consider prenatal screening in this situation.

Conclusions

FMR1 gene mutations commonly result in inherited intellectual disability, infertility, and neurodegeneration syndromes that are encountered by clinicians in a variety of settings. Patients and clinicians are still largely unfamiliar with this disorder, its complicated inheritance, and its heterogeneous phenotype. Debate continues over who should be offered prenatal carrier screening. As more disease screening is offered, pretest counseling will only become more complex and clinicians will further struggle to balance the needs of the individual and allocation of public health resources. If universal prenatal screening is to be adopted, more research is needed regarding patient understanding of the tests they are undergoing, the psychological impact of such screening, and how this knowledge impacts health care and quality-of-life outcomes. ■

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MAIN POINTS

- Fragile X syndrome is the most common inherited form of intellectual and developmental disability worldwide. Unlike other causes of mental retardation such as Down syndrome, phenotypic features of fragile X often are not apparent until later in childhood, making it difficult to diagnose during the newborn period.
- *FMR1* gene mutations commonly result in inherited intellectual disability, infertility, and neurodegeneration syndromes that are encountered by clinicians in a variety of settings. Patients and clinicians are still largely unfamiliar with this disorder, its complicated inheritance, and its heterogeneous phenotype.
- Debate continues over the individuals who should be offered prenatal carrier screening. Current guidelines from the American Congress of Obstetricians and Gynecologists recommend prenatal screening and genetic counseling for fragile X in women with a family or personal history of fragile X, unexplained mental retardation or developmental delay, or premature ovarian insufficiency.
- As more disease screening is offered, pretest counseling will only become more complex and clinicians will continue to struggle to balance the needs of the individual and allocation of public health resources. If universal prenatal screening is to be adopted, more research is needed regarding patient understanding of the tests they are undergoing, the psychological impact of such screening, and how this knowledge impacts health care and quality-of-life outcomes.