When to consider fragile X

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Early menopause or primary ovarian insufficiency should trigger genetic testing

FRAGILE X syndrome (FXS) is an X-linked genetic condition and the most common cause of inherited intellectual disability and single-gene autism spectrum disorder in Australia.

FXS is part of a group of genetic disorders called FMR1-related disorders (FRD). This group also includes fragile X-associated tremor/ataxia syndrome, which generally has an onset of 50+years of age, and fragile X-associated primary ovarian insufficiency (EXPOI).

It is estimated that one in 4000 women have FXS and one in 150 are carriers of a so-called pre-mutation and are at risk of giving birth to a child with the condition.

GPs are well-placed to instigate discussions with at-risk women about genetic testing, at both the preconception and prenatal stages.

FRM1-related disorders are caused by a mutation in the FMR1 gene. This gene produces a protein called FMRP, which is important for brain development. The number of CGG repeats in the FMR1 gene defines the risk of related disorders. CGG repeats over 200 (full mutation) result in the full FXS phenotype in males but in females the effects can vary, from no problems through to full-blown FXS.

Those with CGG repeats between 55 and 200 are classified as having a pre-mutation expansion. This can expand to a full mutation when passed from a carrier mother to her child.

Females with a full mutation or large pre-mutation have a 25% risk of having an affected male child.

HEALTH IMPACT

Young women with the FMR1 pre-mutation are at risk of premature ovarian failure. It is estimated that FXPOI occurs in up to 25% of female carriers of a FMR1 pre-mutation. It can lead to premature menopause, infertility or subfertility, irregular and missed periods, vaginal dryness and insomnia.

FXPOI may be mistaken for early menopause by clinicians who are not familiar with fragile X-associated disorders. However, women with FXPOI can still conceive.

Identifying at-risk women before conception is ideal, as is early referral to a genetic health specialist when a woman is found to be a carrier of a FMR1 pre-mutation.

There are options to prevent the birth of a child with FXS. These include testing an established pregnancy, or testing embryos produced by IVF.

DIAGNOSIS OF DISORDERS

History-taking may help identify undiagnosed carriers of a FMR1 pre- or full mutation. This is done by asking the woman about relatives (of all ages) with learning or developmental delays, autism spectrum disorder or ADHD-like features, emotional or social problems such as shyness or aggression, ataxia, Parkinsonism and balance problems, primary ovarian insufficiency and FMR1-related disorders.

All women with primary ovarian insufficiency should have a DNA test for the CGG repeat length in FMR1, for which there is a Medicare rebate.

Where a woman is identified as having a FMR1 pre-mutation, it is recommended that she be referred for genetic counselling to discuss the diagnosis, her reproductive options and advice about testing of at-risk relatives.

PATIENT RESOURCES

www.genetics.edu.au/
https://fragilex.org.au/

References /further reading at medobs.com.au

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