LETTERS TO THE EDITOR

Fragile X primary ovarian insufficiency

Insuficiencia ovárica primaria asociada al X frágil

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Dear Editor,

We read with great attention the review article on Fragile X Syndrome in children[1] recently published in Colombia Médica. However, we would emphasize the importance of recognizing and addressing the peculiar Fragile X-associated primary ovarian insufficiency.

Actually, premutation of the fragile X messenger ribonucleoprotein 1 (*FMR1*) gene is characterized by an expansion of the CGG trinucleotide repeats (55 to 200 CGGs) in the 5' untranslated region and increased levels of *FMR1* mRNA[2].

Clinically, premutation carriers may exhibit a wide range of symptoms and phenotypes: Fragile X-associated tremor/ataxia syndrome (FXTAS), fragile X-associated neuropsychiatric disorders (FXAND), and the peculiar fragile X-associated primary ovarian insufficiency (FXPOI): a condition that leads to infertility and early menopause in women, as well as irregular menstrual cycles, and is associated with elevated levels of follicle-stimulating hormone (FSH). Studies have also shown that between 12% and 28% of women who are fragile X premutation carriers have primary ovarian insufficiency, and, inversely, this condition is more common in women with the fragile X premutation: females with a premutation in their *FMR1* gene are at a higher risk for primary ovarian insufficiency, with approximately 20% of affected individuals developing this condition over their reproductive lifespan, compared to only 1% in the general population [3].

Genetically, females carrying premutation alleles in the 80-100 CGG range have the highest risk of ovarian dysfunction, estimated at 38% in this high-risk group. A recent, large cross-sectional study involving 1,668 females provided more individualized risk assessments for FXPOI by employing high-resolution repeat-size bins. This intra-population variability in risk has significant implications for genetic counseling, family planning, and future care for premutation carriers [4].

Interestingly, a nationwide register-based study found that genetic disorders and congenital malformations were strongly linked to premature ovarian insufficiency, especially when diagnosed at a young age, and early-onset POI could indicate an underlying genetic disorder like Fragile X syndrome, highlighting the need for further medical evaluations [5].

Clinicians should be aware of this peculiar association of Fragile X with POI to prevent delays in diagnosing and initiating appropriate hormone replacement therapy.

Declaration of AI use

During the preparation of this work, the authors used Perplexity in order to paraphrase and enhance the clarity of the text. After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the publication's content.

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RESPONSE

Authors' response: Fragile X primary ovarian insufficiency

Respuesta de los autores: Insuficiencia ovárica primaria asociada al X frágil

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We are responding to the letter to the editor sent by distinguished readers of our article Fragile X in Children [1]. Their comments are based on the findings reported by Silvén *et al.* in 2023 [2], who found a significant association between genetic disease and/or congenital anomalies and early-onset primary ovarian insufficiency (POI). On this basis, the readers suggest that "Clinicians should be aware of this peculiar association of Fragile X with POI to prevent delays in diagnosing and initiating appropriate hormone replacement therapy."

POI is well documented in women carrying the premutation with alleles between 55 and 200 CGG triplets in the 5' untranslated region of the *FMR1* gene; in these women, POI is found in 20% and is named Fragile X-associated primary ovarian insufficiency (FXPOI), compared with only 1% of women in the general population [3,4].

Although Silvén *et al.* [2] report a significant association between genetic disease and/or congenital anomalies and early-onset POI, they do not refer specifically to cases of ovarian failure in women with the full mutation or with the premutation in the *FMR1* gene. In women with the full mutation, defined as more than 200 repeats of the CGG triplet, with or without intellectual disability, FXPOI has not been described. In the authors' experience, none of approximately 220 women with the full mutation had POI.

We would propose that in those adolescent or young women with genetic diseases and/or congenital anomalies in whom Müllerian anomalies, such as the absence of the uterus, and Turner syndrome have been ruled out, PCR with double or triple primers for the quantification of the triplets in the 5' untranslated region of the *FMR1* gene should be performed to identify whether they have a double genetic hit [5], the second hit being the *FMR1* premutation [6].

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