

# Premature Ovarian Failure: A Phenotypic Expression of Fragile X Premutation

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## Abstract:

Fragile X syndrome is the most common cause of mental retardation in the male. Historically, fragile X premutation was considered to be phenotypically silent. In recent reports the premutation has been associated with premature ovarian failure and fragile X-associated tremor/ataxia syndrome. This case describes a 24-year-old woman who presented with irregular menstrual cycles secondary to premature ovarian failure. Subsequent genetic analysis confirmed that she has a premutation for fragile X with 70 CGG trinucleotide repeats.

## Introduction

Premature ovarian failure (POF) is defined as loss of ovarian function resulting from follicular depletion in a woman less than 40 years of age. This loss of ovarian function can result in infertility as well as vasomotor symptoms, urogenital atrophy and osteoporosis. There are a number of potential etiologies for premature follicular depletion. The causes include: idiopathic, iatrogenic, X chromosomal abnormalities, polyglandular autoimmune failure syndrome and a number of other less common genetic etiologies.<sup>1</sup>

The premutation for fragile X syndrome was long thought to be asymptomatic, but more recently it has been associated with POF and fragile X-associated tremor/ataxia syndrome (FXTAS). FXTAS is characterized by late-onset progressive intention tremor, gait ataxia, peripheral neuropathy and dementia.<sup>2,3</sup>

This case report describes a 24-year-old female with POF who was discovered to have the premutation for fragile X syndrome.

## Case Report

A 24-year-old, nulligravid woman presented with three years of irregular menstrual cycles accompanied by hot flashes. Menarche occurred at age 13, and her menses were regular until three years ago. She has no chronic medical illnesses and has never had surgery. She has smoked approximately a quarter of a pack of cigarettes per day for the last 9 years.

Family history is significant for grandparents with thyroid disease. There is no family history of diabetes mellitus,

pernicious anemia, autoimmune conditions, mental retardation or known fragile X syndrome.

On physical examination the patient was 5 feet, 1.5 inches tall and weighed 131 pounds. Her blood pressure was 119/70. The rest of her physical examination was normal. Pertinent laboratory values included an initial follicle stimulating hormone level of 114 mIU/mL (3-15 mIU/mL) and repeat of 85.4 mIU/mL, luteinizing hormone of 64.3 mIU/mL (1.5-12 mIU/mL), and inhibin B < 30 pg/mL (<30 pg/mL, postmenopausal; <255 pg/mL, premenopausal). Thyroid function tests, fasting glucose, calcium and phosphorous were normal.

The history, physical examination and laboratory data suggested premature ovarian failure. Karyotyping revealed a normal 46,XX female. Molecular testing for fragile X status revealed approximately 70 CGG trinucleotide repeats present on the FMR1 gene, consistent with a premutation for fragile X syndrome.

## Discussion

Fragile X syndrome is the most common cause of mental retardation in the male. The premutation for fragile X syndrome was originally thought to be asymptomatic but has recently been implicated in POF as well as delayed onset of progressive intention tremor, gait ataxia, peripheral neuropathy and dementia. In young women with POF, evaluation for the FMR1 premutation is essential because some of these women will attempt to reproduce. These patients should be made aware of the inheritance pattern of fragile X and the effects it can have on offspring.<sup>3</sup>

Fragile X Syndrome is a trinucleotide repeat disorder,

caused by an expansion of the CGG (cytosine-guanine-guanine) sequence in the FMR1 gene located on the X chromosome. This abnormal CGG expansion associated with hypermethylation results in a silenced FMR1 gene.<sup>4</sup> A normal FMR1 gene has 5 to 40 CGG repeats, 41 to 58 is considered intermediate, the premutation has 59 to 200 copies, and greater than 200 repeats is the full mutation. It is estimated that approximately one in every 800 males and as many as one in every 250 females are carriers.

Fragile X syndrome is inherited in an uncharacteristic X-linked fashion. The unusual nature of the X-linked inheritance is due to expansion of the number of repeats from one generation to the next, which is known as anticipation. Anticipation for the CGG repeat varies depending on whether the carrier is male or female. Males who are premutation carriers are considered transmitting males. When a premutation from a male is transmitted, small increases in repeat number may occur but do not result in full mutations. Occasionally, premutations transmitted from father to daughter may decrease in size. All daughters of transmitting males are premutation carriers.

Females who possess a premutation have a 50 percent chance of transmitting an abnormal allele, whether it is an expanded premutation or full mutation, in any given pregnancy. The premutation often increases in size if passed on to offspring. The risk of a female's premutation being transmitted as a full mutation is influenced by the number of repeats in the premutation.

In this case, the woman had a premutation of 70 CGG repeats on one of her X-chromosomes. This correlates with a risk of approximately 31 percent<sup>5</sup> for an expansion to full mutation in any pregnancy where the premutation is transmitted.

Premature ovarian failure is defined as amenorrhea before the age of 40 years with an elevated FSH level. POF affects about 1 percent of reproductive-age females. The cause of the POF is often not identified.<sup>6,7</sup> In females with the fragile X permutaion, 15 percent to 28 percent develop POF.<sup>8,9</sup> Interestingly, a female with the full mutation for fragile X (greater than 230 repeats) is half as likely to develop premature ovarian failure as the premutation carrier.<sup>10</sup>

Studies have been done to find an association between CGG repeat numbers and age of menopausal onset. The results have shown that the age of menopause steadily decreases in women with 55 to 100 repeats. However, the association is not linear. Once the CGG sequence is expanded to greater than 100 repeats, the average age of menopause begins to increase.<sup>11,12</sup>

Women with FMR1 premutations can have alteration in

ovarian function similar to ovarian aging, even before manifestation of any of the classic symptoms of menopause.<sup>13</sup> Thus, the female may still be able to become pregnant with an increased risk for having a child with fragile X syndrome.

## Conclusion

In summary, we report a young woman with spontaneous premature ovarian failure due to a trinucleotide expansion of the FMR1 gene on the X chromosome. This case illustrates the need to include fragile X premutation testing for young women with premature ovarian failure. The patient and her family members should be counseled regarding potential clinical implications and inheritance of the fragile X premutation, including possible developmental delay, menstrual irregularities and neurological symptoms.

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