

FMR1 Repeat Length in Infertile Women with Primary Ovarian Insufficiency

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Although the current American College of Obstetrics and Gynecology suggests that women with premature ovarian failure (POF) undergo FMR1 premutation testing, the guideline may miss women with infertility in the early stages of POF, here termed premature ovarian insufficiency (POI). Further, recent reports suggest that there is an association between the intermediate size FMR1 allele and POF. We hypothesized that the prevalence of both the FMR1 premutation and the intermediate allele is higher in women with infertility secondary to POI than in controls, even in the absence of family history.

Methods: The subjects were menstruating women <42 years old with POI seen between January, 2006 and October, 2009 at Brigham and Women's or Massachusetts General Hospital infertility centers (n=821). Subjects underwent treatment with clomiphene citrate or gonadotropin stimulation \pm IVF. POI was defined as: 1) elevated FSH (≥ 10 IU/L) on cycle day 2-5 or day 10 of a clomiphene citrate challenge test or at random if cycles were irregular; or 2) normal FSH with an elevated day 2-5 estradiol (>80 pg/ml); or 3) a poor response to gonadotropin stimulation. Subjects were excluded for family history of unexplained mental retardation, autism or fragile X syndrome and abnormal karyotype. Control subjects (n=1398) were women presenting for prenatal genetic counseling who had no family history [1]. Data were also compared to the premutation and intermediate allele prevalence in published data [2].

The largest and smallest allele sizes were compared using a rank sum test. Prevalence of the FMR1 premutation and intermediate size repeat was compared using the Fischer exact test.

Results: FMR1 results were available on 186 women with POI (23%), with repeat number available on 138 (17%). The largest (CGG)n repeat number was higher in women with POI than in control women (31 (30, 32) vs. 30 (30, 31); median (25%, 75% confidence limits); $p < 0.001$). There was no difference in the size of the smallest allele (29 (22, 30) vs. 29 (23, 30) $p = 0.3$). The prevalence of the premutation and intermediate size allele was higher in women with POI compared to controls (**Table 1**).

Table 1	N=	Premutation (55-200)	N=	Intermediate (45-54)
Total Test Results	161	3 (1.86%)	138	6 (4.35%)
Control Data	1398	5 (0.36%)	1398	11 (0.79%)
Fischer Exact		P=0.04		P=0.003
Published Data	9759	38 (0.39%)	9759	183 (1.88%)
Fischer Exact		P=0.03		P=0.05

Conclusions: The data suggest that the prevalence of the premutation is increased in women with POI who present for infertility treatment. Thus, FMR1 screening should be the standard of care for any woman presenting for infertility treatment with POI alone. The data also suggest that the prevalence of the intermediate size allele is also increased. Further studies are needed to determine whether intermediate size alleles play a role in POI.

1. Cronister, A., et al. *Genet Med*, 2005. 7(4): p. 246-50

2. Cronister, A., et al. *Obstet Gynecol*, 2008. 111(3):p. 596-601