



**The 67th Annual Meeting of the Pacific Coast Reproductive Society**  
**April 3-7 2019 • Renaissance Hotel, Indian Wells, California**

**Title:**

IS THERE A CGG REPEAT THRESHOLD TO PREDICT THE RISK OF OCCULT PREMATURE OVARIAN FAILURE IN FRAGILE X PREMUTATION CARRIERS?

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**Background:**

Fragile X premutation carriers are at risk for Fragile X-associated premature ovarian insufficiency (FXPOI).<sup>1</sup> CGG repeat ranges have historically been used to assess the possibility of expansion to full mutation in subsequent generations. Recently, CGG repeats have been considered to be a potential marker of diminished ovarian reserve, albeit no common threshold currently exists to predict a patient's risk for FXPOI.

**Objective:**

The objective of this study is to determine a lower limit cutoff number for CGG repeat length that associates with occult POI.

**Materials and Methods:**

The retrospective, cohort study included all patients who had CGG repeats in the intermediate (45-54) and premutation (55-200) range who presented for assisted reproductive technologies (ART) treatment between the years of 2008 and 2018. Patient age, serum AMH level, and



number of CGG repeats was evaluated. AMH level was treated as a binary measure with 1.0 ng/mL used as a cutoff for diminished ovarian function. Patients were segregated by SART age categories (A: <35; B: 35-37.99; C: 38-40.99; D:41-42.99; E:≥43). A “minimum p-value approach”<sup>2</sup> was used to determine 10 candidate cut-points, and the optimal threshold was chosen by SAS based on a total score assigned based on the corresponding odds ratio estimates and unadjusted p-values. A binary logistic regression was performed to confirm that the CGG threshold was predictive of DOR.

### **Results:**

A total of 255 Fragile X intermediate and premutation carriers with a recorded AMH level were identified. In patients <35 years of age (n=115), we identified 69 CGG repeats as the most significant threshold for predicting diminished ovarian reserve (DOR)(Table 1). The predictive value of this CGG threshold was confirmed in the binary logistic regression model (OR 1.04 [95% CI 1.02-1.06), p=0.001. There was no statistically significant threshold for number of CGG repeats predictive of DOR in older patients (Table 1).

### **Conclusion:**

For patients under the age of 35, a threshold of 69 CGG repeats was associated with a DOR diagnosis. A similar finding was demonstrated in a recent study, which reported patients possessing 70-90 CGG repeats were significantly at risk for lower ovarian reserve.<sup>3</sup> The number of CGG repeats was not a significant predictor of DOR in patients of advanced age. The lack of association between CGG repeat and diminished ovarian reserve in SAR age groups B to E may be explained by the overwhelming influence of ovarian aging which may dilute the relationship. Future genomic studies should aim to elucidate the mechanism by which increased CGG repeat number mediate accelerated follicular depletion and whether CGG repeat number influences proper oocyte meiosis, chromosome segregation, and resulting embryonic ploidy.

### **Financial support:**

None

### **Table 1:**

CGG repeat thresholds by SART age group (A= <35; B= 35-37.99; C=38-40.99; D=41-42.99; E=≥43)



SART Age Group	CGG repeat threshold	Adjusted p-value
A (N=116)	69	0.00005*
B (N=60)	47	1.03423
C (N= 52)	50	1.00040
D (N= 15)	51	0.51781
E (N= 12)	60	0.41667

### **References:**

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2. Williams A, Mandrekar JN, Mandrekar SJ, et al. Finding Optimal Cutpoints for Continuous Covariates with Binary and Time-to-Event Outcomes. Technical Report 2016 Series. 79.
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