J Genet Counsel (2008) 17:84–91
DOI 10.1007/s10897-007-9129-9

ORIGINAL RESEARCH

Emotional Reaction to Fragile X Premutation Carrier Tests Among Infertile Women

Lisa M. Pastore · Wendy L. Morris · Logan B. Karns

Received: 10 April 2007 / Accepted: 21 September 2007 / Published online: 30 October 2007

Abstract Female fragile X premutation carriers are at ~10-fold increased risk of premature ovarian failure (follicle stimulating hormone >40 mIU/mL, amenorrhea, age <40). A milder degree of premature ovarian aging (diminished ovarian reserve, where follicle stimulating hormone levels are typically 10–20 mIU/mL) results in infertility. Approximately 10% of fertility clinic patients have this diagnosis. A cohort of 20 women diagnosed with diminished ovarian reserve provided a blood specimen (confidential results), and completed structured questionnaires that assessed emotional reactions to potentially being a premutation carrier (pretest questionnaire, $n=20$) and the posttest known carrier status (3 month follow-up questionnaire, $n=18$ non-carriers). Responses were measured using 9-point scales, and analyzed with Fisher exact and Wilcoxon exact tests. While most participants did not view fragile X premutations as a serious medical condition, perceptions of seriousness were positively correlated with anger and regret about not knowing sooner of the potential association of these premutations with infertility. Overall, when women (pretest) imagined themselves as carriers, their self-esteem and Health Orientation Scale responses were unchanged with the exception of feeling more afraid ($p=0.004$). Despite strongly wishing for negative test results, they were glad to know there might be a medical explanation for their infertility.

Keywords Diminished ovarian reserve · Fragile X · Genetic counseling · Genetic screening · FMR1 gene · Emotions · Infertility · Female

Financial Support: This work was financially supported by a University of Virginia School of Medicine Research & Development Award.

L. M. Pastore · L. B. Karns
Department of Obstetrics and Gynecology, School of Medicine, University of Virginia,
Charlottesville, VA, USA

W. L. Morris
Department of Psychology, McDaniel College,
Westminster, MD, USA

L. M. Pastore (✉)
OB/GYN Department, University of Virginia,
Box 800712, Charlottesville, VA 22908-0712, USA
e-mail: lpastore@virginia.edu

Introduction

Fragile X syndrome is the most common heritable form of mental retardation in males. Individuals with fragile X syndrome have a CGG trinucleotide expansion in the 5′-untranslated region of the Fragile X Mental Retardation (FMR1) gene. While the normal number of repeats in this area is less than 50, individuals with fragile X syndrome have an expansion of over 200 repeats, referred to as a full mutation. An intermediate expansion, termed a premutation, exists between 55–200 repeats. Both males and females can be carriers of a fragile X premutation. Until recently, these premutation carriers had been considered phenotypically normal, due to the lack of mental retardation or other manifestations of the fragile X phenotype. However, there is now evidence that the premutation alleles themselves have clinical correlates. Males with premutation alleles are at increased risk of fragile X-associated tremor/ataxia syndrome (Hagerman and Hagerman 2004). Females with premutations are at ~10-fold increased risk of premature ovarian failure (POF) (Sullivan *et al*. 2005), which is diagnosed by amenorrhea and postmenopausal levels of follicle stimulating hormone (FSH) before the age of 40.

In the United States, the incidence of infertility among reproductive age women is approximately 10% (Stephen and Chandra 2000). About 10% of these women are diagnosed with diminished ovarian reserve based on elevated levels of FSH (Levi *et al*. 2001; Scott *et al*. 1995), but not elevated to the degree of women with POF. Women with diminished ovarian reserve still have regular menses, as opposed to women with POF who are amenorrheic. Few women with diminished ovarian reserve (<5%) will become pregnant spontaneously and they do not respond normally to fertility drugs. For the vast majority of women diagnosed with this condition, the etiology remains unknown (Speroff and Fritz 2005).

Female premutation carriers may exhibit a range of endocrine irregularities, and thus it has recently been recommended that the term "fragile X-associated primary ovarian insufficiency" be used (McConkie-Rosell *et al*. 2007). The evidence documenting the relationship between fragile X premutations and diminished ovarian reserve is limited, even though this association is a logical extension from the prior research involving women with POF (S. L. Sherman 2000). There are four reports that document ovarian hormone dysfunction (primarily elevated FSH) in women with fragile X premutations (Braat *et al*. 1999; Murray *et al*. 1999; Sullivan *et al*. 2005; Welt *et al*. 2004), and the authors of this report are currently conducting research on the prevalence of fragile X premutations among infertile women. The American College of Medical Genetics (ACMG) has issued a policy statement that recommends fragile X testing for "women with reproductive or fertility problems associated with elevated FSH levels, especially if there is a family history of premature ovarian failure, fragile X syndrome, or undiagnosed mental retardation" (S. Sherman *et al*. 2005), and the Genetics Committee of the American College of Obstetrics & Gynecology supports this recommendation (ACOG Committee on Genetics 2006). The ACMG recommendation regarding fragile X testing for infertile women with high FSH levels is based on research involving women with fragile X-associated primary ovarian insufficiency (S. L. Sherman 2000).

Despite these recommendations, there is no data regarding the emotional reactions of women with infertility to fragile X premutation testing. Reactions to fragile X carrier testing have been conducted among several other groups including (1) members of fragile X syndrome families (n=20 carriers and n=22 non-carriers from 17 families) using a visual analog scale tool (McConkie-Rosell *et al*. 2001), (2) focus groups of premutation carriers (n=18) from fragile X syndrome families (Anido *et al*. 2005), (3) adults at risk for any of 4 autosomal-recessive and X-linked-recessive disorders including fragile X syndrome (n=34) using qualitative interviews (Williams and Schutte 1997), (4) general population focus groups of women (n=13) not at risk to be carriers of fragile X mutations (Anido *et al*. 2005), and (5) premutation carriers without a family history of fragile X syndrome who were identified through general population screening (n=8) (Anido *et al*. 2007). Those reports found that being at-risk to be a carrier for a genetic disorder is an upsetting state (McConkie-Rosell *et al*. 2001), women had active coping mechanisms but also had concerns for the implications of their carrier status for their children or grandchildren (Anido *et al*. 2005; McConkie-Rosell *et al*. 2001), the results impacted reproductive decisions whether in hindsight or for their own future (Anido *et al*. 2005; McConkie-Rosell *et al*. 1997; Williams and Schutte 1997), and the women's positive carrier status generally had minimal relevance unless it pertained to a current stage of life (Anido *et al*. 2007).

Given the recent recommendations that women with elevated FSH levels for their age receive fragile X testing, it is important to understand how infertile women perceive this genetic test. This is the first report describing the emotional reactions of fertility clinic patients to fragile X carrier testing. This study assessed pretest perceptions of fragile x testing, emotional reactions to potentially being a premutation carrier including how it might affect feelings about infertility, and emotional reactions to a negative test result in a population of women diagnosed with diminished ovarian reserve.

Materials and Methods

All study participants were female, diagnosed with diminished ovarian reserve by the University of Virginia (UVa) OB/GYN Department or a local private reproductive endocrinology practice, aged 18–42 years at the time of their diagnosis, and mentally capable of making informed decisions. The women in this study were infertile with regular menstrual cycles, but diagnosed with an elevated menstrual cycle day 2–5 FSH>10 mIU/mL or a positive clomiphene citrate challenge test (Speroff and Fritz 2005). Women were excluded if they had a family history of the fragile X syndrome (full mutation). The UVa Institutional Review Board approved this study.

A cohort of eligible infertile women was identified both prospectively and retrospectively. Most women were identified by self-nomination after participating in a prior fragile X premutation study that did not involve blood sampling (Pastore *et al*. 2006) or physician referral from a local private reproductive endocrinology practice. Women were mailed an invitation to be in the study, and had the option to participate without learning their genetic test results. Included in this invitation packet was a two-page educational brochure on fragile X premutations for OB/

GYN patients (Pastore *et al*. 2006). No pretest genetic counseling was offered through the study protocol. At the study visit, informed consent was obtained, blood was drawn, and questionnaires were administered. All materials were coded with an assigned ID to maintain anonymity.

Two questionnaires were self-administered at baseline/pretest to assess these topics: (1) family history of infertility, early menopause, mental retardation, and tremors; (2) infertility and related treatment history; (3) smoking history; (4) demographics, such as age, race, education; (5) self-esteem using a slightly reworded version of the classic Rosenberg tool (Rosenberg 1986); (6) the Health Orientation Scale (Wooldridge and Murray 1988), which measures the psychological implications of being identified as a carrier of a genetic mutation; (7) level of upset and perception of seriousness regarding fragile X premutations (McConkie-Rosell *et al*. 2001); and (8) a series of questions developed by the authors (WLM, LMP, LBK) specifically for women with diminished ovarian reserve who were undergoing this testing regarding their feelings of stigmatization, importance of having biological children, importance of having a medical explanation of fertility, anger and regret over not learning about fragile X sooner, and communication to others about consenting to testing. Items 6, 7 and 8 were only posed to the participant if she wanted to learn her fragile X test results, which was true for 18/20 women in this study. This manuscript focuses on the pretest responses from these 18 women, which includes the 1 identified carrier. A subset of the questions (items 5–8) was repeated 3 months after the participant learned her test results, resulting in a population of 17 non-carrier women for longitudinal analyses.

All emotions and opinions were measured using 9-point scales where 1=not at all and 9=very much. Exact Mann–Whitney U or signed rank nonparametric statistics (Wuensch 2004) were used to compare the self-esteem, Health Orientation Scale, and any other scale question where there were paired results. The paired comparisons included: (a) pretest baseline perceptions vs. pretest imagined positive ("if you were found to be a carrier..."), (b) pretest baseline perceptions vs. 3 month follow-up, and (c) pretest imagined positive vs. 3 month follow-up projection as to how she thinks others feel who are carriers of fragile X premutations ("instead of describing your own feelings, please tell us how you think most people who are carriers of a fragile X premutation would describe THEIR feelings"). McNemar tests were used to compare the communication-related questions between baseline and baseline imagined positive. Based on the results of a factor analysis, two questionnaire responses were combined into a composite score: "I am glad to know that there may be a medical reason for my infertility" and "I feel better about my infertility since learning there is a medical explanation for my infertility" (reliability=0.79 and 0.85 at baseline and follow-up, respectively). All statistical analyses were based on two-sided tests with an alpha level of 0.05.

Results

The mean age of the participants was 39.5 years (range of 32–44) at the time of the study (as opposed to the age at the initial diminished ovarian reserve diagnosis, which ranged from 32 to 42), and 15% were non-white (Table I). The testing identified one premutation carrier (1/20=5%) with allele sizes of 23 (normal) and 77 (premutation); she declined additional genetic counseling after an initial telephone discussion of her test result with a genetic counselor. All other results were within normal limits with a minimum repeat length of 18, maximum of 39, and median of 28. All but two participants wanted to know their test result (as opposed to donating the blood for research purposes only).

Perceptions About Fragile X Premutations and Carrier Testing

Participants overall had no strong feelings in either direction as to their likelihood of being a carrier at baseline (mean 4.5, Table II), although three women selected "very unlikely" (score ≤2) as their response. They were glad to know there might be a reason for their infertility (mean 7.8), and their feelings did not significantly change in this regard with a projected positive carrier status.

There was great variability in whether or not they viewed a fragile X premutation as a serious medical condition (mean 5.44, sd 2.38), with two women reporting

Table I Characteristics of the Participants (n=20)

Factor	*N* (%)
Age at survey (years)	Mean 39.5 (sd 3.0) Median 40.0 Range 32–44
Non-Caucasian race	3 (15%)
Nulliparous	8 (40%)
BMI	Mean 24.8 (sd 5.1) Median 22.6 Range 19.7–34.2
Ever smoked	4 (20%)
Self-reported age when woman first spoke to doctor about fertility difficulty (missing n=1; years)	Mean 35.1 (sd 2.5) Median 35.0 Range 30–40
Family History	
Mental retardation	1 (5%)
Down syndrome	0 (0%)
Physical tremors among older relatives	4 (20%)

Table II Pretest Responses to Selected Questions

	Baseline (pretest)	
	Mean	Standard Deviation
"How likely do you think it is that you are a carrier of a fragile X premutation?"	4.50	1.76
"I'm glad to know there may be a reason for my infertility."	7.78	1.93

Sample: $N=18$ women who wanted to know their fragile X test results
1=not at all; 9=very much

"not serious at all" (scores ≤2), four women reporting "very serious" (scores ≥8), and the remaining 12 women falling between these two extremes (Fig. 1). The extent to which the women believed that fragile X premutations were very serious at baseline was positively related to feeling more angry ($p=0.013$) and regretful ($p=0.005$) that they did not know sooner that fragile X might be related to infertility (Table III). No demographic (as listed in Table I) or reproductive history factor (age at menarche, current menopausal status, family history of infertility or early menopause) was significantly associated with perceived seriousness of fragile X premutations, although two approached significance and should be investigated in future research: first or second degree family history of infertility ($p=0.05$) and perimenopausal status ($p=0.08$). Perception of the seriousness of fragile X premutations increased 3 months after learning they were not a carrier but this did not quite reach statistical significance (mean 6.7, sd 1.7, $p=0.06$, Fig. 1).

Five women (25%) reported that they had learned that fragile X premutations might increase the risk of infertility prior to being invited to participate in this study, despite the fact that 11 of the participants had participated in a 2004 UVa fragile X research study that did not involve blood testing (Pastore *et al*. 2006). The reported sources of prior knowledge were: participation in the 2004 UVa study ($n=2$), her physician ($n=2$), and independent investigation by the participant ($n=1$). While non-carrier women were not initially very angry or regretful that they did not know sooner that fragile X premutations might be related to infertility (mean 2.16 and 3.21, respectively), three months later they thought carriers would be more angry ($p=0.02$) and regretful ($p=0.03$) than they felt themselves (Table IV).

Projections of How Women Think They Would Feel if They Were Carriers

When women imagined they were carriers, 5/16 women predicted they would be strongly upset (scores ≥8) if they found out that fragile X ran in their family and that they "could have a child or grandchild with fragile X" (syndrome or premutation), and this was related to perceived seriousness of fragile X premutations, as discussed earlier (Table IV). Two-thirds of participants ($n=10/15$) were neutral on whether or not their blood relatives would be upset if fragile X (syndrome or premutation) ran in their family, almost one-third thought the relatives would not be upset at all, and one woman thought her relatives would be very upset.

Participant predictions, if they were found to be a carrier of a fragile X premutation, are displayed in Table V. These women would strongly wish they were not a carrier (mean 8.3). They predicted that a fragile X premutation would have "little to do with" how they feel about themselves (mean 8.0), would not be an "important reflection" of who they are (mean 1.4), and would not be an important part of their self-image (mean 1.5). Most participants ($n=14/18$) reported that a fragile X premutation would be "unrelated to her sense of self" while four women strongly felt that it would be related to her sense of self. Most of the respondents ($n=14/15$) projected that if they were a carrier, they would feel better about their infertility knowing there is a medical explanation for it.

The participants had high self-esteem and projected that this would not change if they were carriers (Table VI). For the $n=18$ women who answered both the baseline and

Table III Relationship Between Selected Variables and Pretest Perceived Seriousness of Fragile X Premutations

Emotion	Percentage who reported this emotion among women who consider premutations very serious	Percentage who reported this emotion among all other participants	*p*-value **
Somewhat/very regretful that she did not learn sooner that fragile X might be related to infertility, (score ≥5)	7%	75%	0.005
Somewhat/very angry that she did not learn sooner that fragile X might be related to infertility, (score ≥5)	0%	50%	0.013
Very upset "if you found out that fragile X runs in your family and that you could have a child or grandchild with fragile X", (score ≥8)	100%	8%	0.002

** Continuous variable used for statistical comparisons (exact Wilcoxon test)
Sample: $N=18$ women who wanted to know their fragile X test results

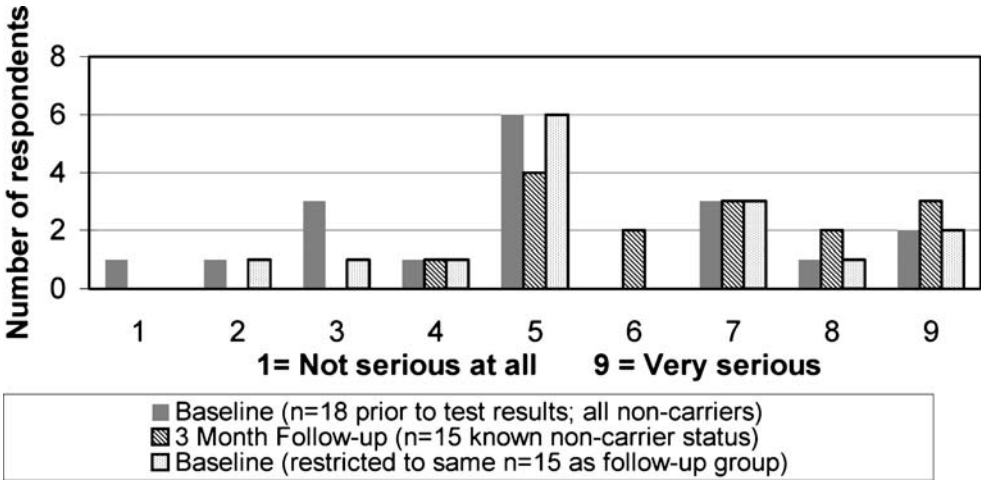

Fig. 1 How serious do you think fragile X premutations are as a medical condition?

"baseline imagined positive" questions, the mean baseline self-esteem score of the participants was 8.38 (sd 0.61) where 1=low self-esteem and 9=high self-esteem, with a range of 6.9–9.0. Their self-esteem was essentially unchanged when these women imagined themselves to be carriers (mean 7.96, sd 1.35; $p=0.27$) and 3 months after learning they were not carriers (mean 8.0, sd 1.2, $p=0.10$). When women at baseline imagined themselves to be carriers, they predicted that they would not feel differently about themselves as measured by the Health Orientation Scale with the exception of feeling more afraid ($p=0.004$).

Feelings About Having Future Biological Children

It was equally important to the participants "to have a (or another) biological child in the future" at baseline and three months later (means 6.9–7.0). These means did not differ by parity at baseline ($p=0.86$), but 3 months later this was more important to nulliparous women than parous women (mean 8.4 vs. 6.4, respectively, $p=0.038$). Forty percent of the participants were nulliparous. If she were found to be a carrier, almost half of the women (7/16) projected that they would be less likely to have a biological child in the future, while the remaining nine women were neutral on this question, and this did not vary by parity ($p=0.33$).

Sharing Information with Family Members and Friends

Most women (83%) told their partner that they were undergoing the test. One-third of the participants told their parents and/or their friends that they were undergoing this test, while 17% had shared this information with siblings or extended family members. When women imagined themselves as carriers, all reported they would tell their romantic partner about the test results, 83% would tell their parents, 72% would tell their sibling(s), 61% would tell friend(s), and 39% would tell their extended family. The latter three results are statistically different than the proportions of women who had informed those people that they were being tested through this study (all $p<0.05$).

Table IV Pretest vs. Follow-up Responses on Anger and Regret

	Baseline (pretest)*		Baseline (pretest)**		3 Month Follow-up Projection "if they were a carrier"**		P-value**
	Mean	sd	Mean	sd	Mean	sd	
Anger that she did not learn sooner that fragile X might be related to infertility	2.16	2.14	2.29	2.23	4.41	2.45	0.02
Regret that she did not learn sooner that fragile X might be related to infertility	3.21	2.88	3.12	2.85	5.41	2.98	0.03

sd=standard deviation; 1=not at all; 9=very much

* Sample: $N=19$ non-carrier women, including those who did not want to know their fragile X test results

** Sample: $N=17$ non-carrier women, excluding two women who did not receive follow-up questionnaire because they did not want to know their fragile X test results

Table V Pretest Predictions About Emotions When Women Imagined Themselves to be a Premutation Carrier

	Baseline (pretest)	
	Mean	Standard Deviation
I wish I were not a fragile X carrier.	8.28	1.18
Overall, being a carrier has very little to do with how I feel about myself.	8.00	1.97
Being a carrier is an important reflection of who I am.	1.39	1.42
Being a carrier is unrelated to how I see myself (my sense of self).	6.78	3.25
In general, being a carrier is an important part of my self-image.	1.50	1.04
I'm glad to know that there is a medical explanation for my infertility.	8.00	2.06
I feel better about my infertility since learning there is a medical explanation for my infertility.	6.89	2.81

Sample: N=18 women who wanted to know their fragile X test results
1=not at all; 9=very much

Discussion and Implications

Our study results indicate a positive reaction to fragile X premutation testing among infertile women attending a fertility clinic. Before they knew their results, the study participants were glad to know there might be a reason for their infertility and they predicted that being a carrier would make them feel better about their infertility. These women desired an explanation for their infertility and they perceived this test as a way to feel better about their inability to conceive. Three months after being tested, they projected that women who are carriers probably would feel angry and regretful that they didn't know about the relationship between fragile X premutations and infertility earlier. Thus, the participants in this study felt that the information this test provides is important for women to have at the earliest possible point in their infertility evaluation.

It is important to note that although the women projected they would feel better about their infertility if they were carriers, they also reported that if they were carriers they would strongly wish they were *not* carriers. This finding is consistent with past research showing that being a potential carrier is upsetting (McConkie-Rosell *et al*. 2001).

Perceptions of the seriousness of fragile X premutations ranged widely amongst the cohort. Not surprisingly, the women who perceived these premutations as a serious medical condition also reported feeling more angry and regretful about not learning sooner about fragile X, and predicted they would be upset to learn that fragile X (syndrome or premutation) might run in their family. Overall, this population of women with infertility did not perceive fragile X premutations as being as serious as members of fragile X syndrome families (mean 6.9 on a 0–10 visual analog scale) (McConkie-Rosell *et al*. 2001).

It was surprising that only two women reported learning of the potential relationship between fragile X premutations and infertility prior to participation in this study, considering that 11 (55%) of the participants had participated in a previous fragile X study at this institution that did not involve blood testing (Pastore *et al*. 2006). This may indicate the need for repeated communication to patients or face-to-face counseling in addition to written material. There could also be a "disconnect" between reading material, such as the educational brochure, and the actual pursuit of genetic testing, with the latter being a much more personal and pertinent source of retained knowledge.

Limitations

The primary strength of this research is that it provides important information relevant to recent medical recommendations. Specifically, how do infertile women feel about fragile X testing, which is a topic that has not previously been studied and reported. A limitation of this study is that we measured women's projections about how they think they would feel if they were to test positive rather than their actual experiences of testing positive. However, given that most women affected by the recommendations for fragile X testing will have negative test results, it is important to understand how these women feel

Table VI Pretest Self-Esteem and Health Orientation Questionnaire Data

	Baseline (pretest)		Imagine Positive (pretest)		p-value*
	Mean	Standard Deviation	Mean	Standard Deviation	
Rosenberg Self-Esteem	8.38	0.61	7.96	1.35	0.27
Health Orientation Scale					
Good	5.56	1.94	4.39	2.17	0.08
Unafraid	7.22	2.21	5.22	2.92	0.004**
Not guilty	8.33	1.28	7.94	1.80	0.55
Unashamed	8.44	1.29	7.78	2.02	0.25
Strong	7.33	1.71	6.94	2.31	0.51
Relieved	5.56	1.69	5.72	2.80	0.88
Happy	5.00	1.91	4.17	2.33	0.07
Able	6.72	2.30	7.17	2.09	0.59
Pleased	5.50	1.34	5.22	2.13	0.65
Healthy	7.11	1.94	7.11	2.05	1.00
Unstigmatized	7.56	1.85	7.06	2.34	0.17

* calculated from paired signed rank statistics. ** P< 0.05
Sample: N=18 women who wanted to know their fragile X test results
1=negative emotion; 9=positive emotion

about receiving a potentially positive test result when they initially make the decision to undergo testing.

Another limitation is the small sample size of our study, although it is comparable to other similar studies (Anido *et al*. 2005; McConkie-Rosell *et al*. 2001; Williams and Schutte 1997). Our observations are further limited by the patient population of fertility clinics, who are generally in higher socioeconomic groups. Fifteen percent of the participants were non-Caucasian, which accurately represents our fertility population and is fairly close to demographics of the population in the vicinity of the University of Virginia (20.3% in 2005)("Virginia NCHS abridged-race population estimates 2007"). Our questions regarding fragile X "running in the family" did not distinguish between fragile X syndrome and premutations; it is unknown whether patients would have answered more-specifically worded questions differently. Lastly, our sample only included women who chose to be tested.

Conclusions

The significance of the fragile X premutation testing for individual women who are still seeking conception with their own ovum cannot be understated. While premutation carriers do not have fragile X syndrome, they can pass the full mutation to their children. The likelihood of a carrier mother passing the full mutation to her child(ren) increases with the size of her premutation allele, especially if she has at least 100 CGG repeats in the FMR1 gene (Nolin *et al*. 2003). Contractions in the size of the premutation are also possible in the subsequent generation (Brown *et al*. 1996; Fisch *et al*. 1995; Nolin *et al*. 1996; Reyniers *et al*. 1993; Vits *et al*. 1994). Provision of information regarding the chance of having a son with fragile X syndrome or a daughter with the full mutation or a premutation would likely have a significant impact on reproductive decisions made by women with diminished ovarian reserve.

We anticipated that women with fertility difficulties would react very differently to this genetic testing process than families with fragile X syndrome, where the impact of the full mutation is readily apparent. Infertile women seek medical intervention because they want to become pregnant, and are unlikely to anticipate that their infertility is related to a genetic condition. They often have undergone months and years of unsuccessful fertility treatment and tests, and may consider this test to be "at long last an explanation for my infertility." These patients enter the genetic testing process from an initially complex emotional state (Greil 1997; Imeson and McMurray 1996), and without anticipation that their genes may be a key factor underlying their infertility. As this population has not been previously studied for reactions to carrier testing, we believe this study will provide new and valuable insights to clinicians and genetic counselors regarding fragile X premutation testing among fertility clinic patients.

Acknowledgements The Research & Development Committee of the School of Medicine at the University of Virginia provided funding for this study. We are grateful for the assistant of Teresa Camp (research assistant, informed consents), Heidi Flanagan (research nurse), Renata Ornelas (research nurse), Anna Wyse (research nurse), and Kelly Gurka (statistical assistance). We also thank the members of our research team that are not co-authors on this particular manuscript: Dr. Lawrence Silverman (UVa), Dr. Devereux N. Saller (UVa), and Dr. Christopher Williams (private practice).

References

ACOG Committee on Genetics (2006). Screening for fragile X syndrome. *Obstetrics & Gynecology*, *107*(6), 1483–1485.

Anido, A., Carlson, L. M., & Sherman, S. L. (2007). Attitudes toward fragile X mutation carrier testing from women identified in a general population survey. *Journal of Genetic Counseling*, *16*(1), 97–104.

Anido, A., Carlson, L. M., Taft, L., & Sherman, S. (2005). Women's attitudes toward testing for fragile X carrier status: A qualitative analysis. *Journal of Genetic Counseling*, *14*(4), 295–306.

Braat, D. D., Smits, A. P., & Thomas, C. M. (1999). Menstrual disorders and endocrine profiles in fragile X carriers prior to 40 years of age: A pilot study. *American Journal of Medical Genetics*, *83*, 327–328.

Brown, W. T., Houck Jr., G. E., Ding, X., Zhong, N., Nolin, S., Glicksman, A., et al. (1996). Reverse mutations in the fragile X syndrome. *American Journal of Medical Genetics*, *64*(2), 287–292.

Fisch, G. S., Snow, K., Thibodeau, S. N., Chalifaux, M., Holden, J. J., Nelson, D. L., *et al.* (1995). The fragile X premutation in carriers and its effect on mutation size in offspring. *American Journal of Human Genetics*, *56*(5), 1147–1155.

Greil, A. L. (1997). Infertility and psychological distress: A critical review of the literature. *Social Science and Medicine*, *45*(11), 1679–1704.

Hagerman, P. J., & Hagerman, R. J. (2004). The fragile-X premutation: A maturing perspective. *American Journal of Human Genetics*, *74*(5), 805–816 [erratum appears in am j hum genet. 2004 aug;75(2):352].

Imeson, M., & McMurray, A. (1996). Couples' experiences of infertility: A phenomenological study. *Journal of Advanced Nursing*, *24*(5), 1014–1022.

Levi, A. J., Raynault, M. F., Bergh, P. A., Drews, M. R., Miller, B. T., & Scott Jr., R. T. (2001). Reproductive outcome in patients with diminished ovarian reserve. *Fertility & Sterility*, *76*(4), 666–669.

McConkie-Rosell, A., Abrams, L., Finucane, B., Cronister, A., Gane, L. W., Coffey, S. M., *et al.* (2007). Recommendations from multi-disciplinary focus groups on cascade testing and genetic counseling for fragile X-associated disorders. *Journal of Genetic Counseling*, *in press*.

McConkie-Rosell, A., Spiridigliozzi, G. A., Iafolla, T., Tarleton, J., & Lachiewicz, A. M. (1997). Carrier testing in the fragile X syndrome: Attitudes and opinions of obligate carriers. *American Journal of Medical Genetics*, *68*(1), 62–69.

McConkie-Rosell, A., Spiridigliozzi, G. A., Sullivan, J. A., Dawson, D. V., & Lachiewicz, A. M. (2001). Longitudinal study of the carrier testing process for fragile X syndrome: Perceptions and coping. *American Journal of Medical Genetics*, *98*, 37–45.

Murray, A., Webb, J., MacSweiney, F., Shipley, E. L., Morton, N. E., & Conway, G. S. (1999). Serum concentrations of follicle stimulating hormone may predict premature ovarian failure in fraxa premutation women. *Human Reproduction*, *14*(5), 1217–1218.

Nolin, S. L., Brown, W. T., Glicksman, A., Houck Jr., G. E., Gargano, A. D., Sullivan, A., *et al.* (2003). Expansion of the fragile X CGG repeat in females with premutation or intermediate alleles. *American Journal of Human Genetics*, *72*(2), 454–464.

Nolin, S. L., Lewis 3rd, F. A., Ye, L. L., Houck Jr., G. E., Glicksman, A. E., Limprasert, P., *et al.* (1996). Familial transmission of the FMR1 CGG repeat. *American Journal of Human Genetics*, *59* (6), 1252–1261.

Pastore, L. M., Karns, L. B., Pinkerton, J. V., Silverman, L. M., Williams, C. D., & Camp, T. R. (2006). Acceptance of fragile X premutation genetic screening in women with ovarian dysfunction. *American Journal of Obstetrics and Gynecology*, *194*(3), 738–743.

Reyniers, E., Vits, L., De Boulle, K., Van Roy, B., Van Velzen, D., de Graaff, E., *et al.* (1993). The full mutation in the FMR-1 gene of male fragile X patients is absent in their sperm. *Nature Genetics*, *4*(2), 143–146.

Rosenberg, M. (1986). *Conceiving the self*. Malabar, FL: Krieger.

Scott Jr., R. T., Opsahl, M. S., Leonardi, M. R., Neall, G. S., Illions, E. H., & Navot, D. (1995). Life table analysis of pregnancy rates in a general infertility population relative to ovarian reserve and patient age. *Human Reproduction*, *10*(7), 1706–1710.

Sherman, S. L. (2000). Premature ovarian failure in the fragile X syndrome. *American Journal of Medical Genetics*, *97*, 189–194.

Sherman, S., Pletcher, B. A., & Driscoll, D. A. (2005). Fragile X syndrome: Diagnostic and carrier testing. *Genetics in Medicine*, *7* (8), 584–587.

Speroff, L., & Fritz, M. A. (2005). *Clinical gynecologic endocrinology and infertility* (7th ed.). Philadelphia: Lippincott Williams & Wilkins.

Stephen, E. H., & Chandra, A. (2000). Use of infertility services in the United States: 1995. *Family Planning Perspectives*, *32*(3), 132–137.

Sullivan, A. K., Marcus, M., Epstein, M. P., Allen, E. G., Anido, A. E., Paquin, J. J., *et al.* (2005). Association of FMR1 repeat size with ovarian dysfunction. *Human Reproduction*, *20*(2), 402–412.

Virginia NCHS Abridged-Race Population Estimates. Retrieved 03-21-2007, from http://www.vdh.state.va.us/HealthStats/stats.asp.

Vits, L., De Boulle, K., Reyniers, E., Handig, I., Darby, J. K., Oostra, B., *et al.* (1994). Apparent regression of the CGG repeat in FMR1 to an allele of normal size. *Human Genetics*, *94*(5), 523–526.

Welt, C. K., Smith, P. C., & Taylor, A. E. (2004). Evidence of early ovarian aging in fragile X premutation carriers. *Journal of Clinical Endocrinology and Metabolism*, *89*(9), 4569–4574.

Williams, J. K., & Schutte, D. L. (1997). Benefits and burdens of genetic carrier identification. *Western Journal of Nursing Research*, *19*(1), 71–82.

Wooldridge, E. Q., & Murray, R. F. J. (1988). The health orientation scale: A measure of feelings about sickle cell trait. *Social Biology*, *35*(1–2), 126–136.

Wuensch, K. L. (2004). Nonparametric statistics. Retrieved 01-12-2005, from http://core.ecu.edu/psyc/wuenschk/StatsLessons.htm.