Longitudinal Interviews of Couples Diagnosed with Diminished Ovarian Reserve Undergoing Fragile X Premutation Testing

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Abstract:

About 10 % of infertile/subfertile women are diagnosed with diminished ovarian reserve (DOR), of which < 5 % will become pregnant spontaneously. Fragile X (FMR1) genetic testing may provide a reason for her early ovarian aging and/or have reproductive implications. Seven women with DOR (genetic study subset) and the male partners of six of these women were separately interviewed about the experience of being asked to undergo this unanticipated genetic test. Three interviews were conducted (before, within 1 week after, and 3 months after learning the test results). None of the participants carried the FMR1 premutation (largest FMR1 allele 27–50 CGG repeats). For women, their pregnancy-seeking journey was long and exhausting. Women understood the reproductive implications of carrying the FMR1 premutation, and hoped for a negative result. Being offered a genetic test caused women to pause and re-think their future reproductive plans. Husbands viewed the infertility journey as filled with unknowns, of which the genetic test results would be one more puzzle piece. The expense of fertility testing/treatment was mentioned by both spouses, though more notably by husbands. The introduction of a possible genetic cause of infertility, with additional potential health consequences for future biological children, caused women to re-think their quest for pregnancy. In contrast, the genetic test was viewed as an additional source of information for their husbands as opposed to raising concern regarding potential reproductive ramifications.

Keywords: Fragile X | FMR1 | Genetic testing | Qualitative research | Female infertility | Genetic counseling | Diminished ovarian reserve | Decision-making

Article:

Introduction

Fragile X Syndrome (FXS) is the most common heritable form of mental impairment. The molecular cause of this abnormality is an expansion of over 200 (CGG) trinucleotide repeats ("full mutation") within the 5′-untranslated region of the fragile X mental retardation 1 (FMR1) gene. While individuals with a premutation test result (55–199 CGG repeats) do not have FXS, premutations have reproductive implications for both males and females. The likelihood of a mother with the FMR1 premutation passing the full mutation to her children increases with the size of her premutation allele. If the mother has approximately 100 repeats of the CGG genetic sequence in the FMR1 gene, there is a nearly 100 % chance that her child(ren) will have the full mutation (Nolin et al. *2003*, *2011*). Risk of expansion to the full mutation is moderated when the FMR1 CGG repeat is interspersed with one or more AGG's (Nolin et al. *2013*). Contractions of the FMR1 gene have also been reported (Brown et al. *1996*; Fisch et al. *1995*; Nolin et al. *1996*; Reyniers et al. *1993*; Vits et al.*1994*). Premutation males very rarely pass on a full mutation to their offspring (Ashley-Koch et al. *1998*; Zeesman et al. *2004*).

FMR1 repeat lengths have also been linked with primary ovarian insufficiency (POI), which is a term that represents a broad clinical spectrum related to early aging of the ovaries (McConkie-Rosell et al. *2007*). Diminished ovarian reserve (DOR) and premature ovarian failure (POF) both fall within the definition of POI. DOR typically presents clinically as infertility, while POF presents as a cessation of menses. POF is related to DOR in that both are diagnosed by high follicle stimulating hormone (FSH) levels (>40 IU/L for POF (Nelson and Bakalov *2003*) vs. > 10 IU/L in cycle days 2–4 for DOR (Speroff and Fritz *2005*)). A POF diagnosis requires that the woman be less than 40 years old and have 4 or more months of secondary amenorrhea (Nelson and Bakalov *2003*), while DOR women are still menstruating and no age limit is applied. DOR is a normal physiologic process when it occurs in the mid to late forties, and is pathological at younger ages. Approximately 10 % of women seeking fertility assistance are diagnosed with DOR (Levi et al. *2001*). There is evidence that women with the premutation (Karimov et al. *2011*; Sherman *2000*), and potentially women with high normal (Pastore et al. *2012*; Streuli et al. *2009*) or intermediate (Gleicher et al. *2009*; Karimov et al. *2011*) level repeats (35–44 and 45–54 CGG repeats, respectively), have an increased risk of POI.

The American College of Medical Genetics (ACMG) testing guidelines recommend FMR1 testing for "women with reproductive or fertility problems associated with elevated FSH levels, especially if there is a family history of POF, FXS, or undiagnosed mental retardation" (Sherman et al. *2005*). The National Society of Genetic Counselors and the Genetics Committee of the American College of Obstetrics & Gynecology support this recommendation (ACOG Committee of Genetics *2010*; Finucane et al. *2012*), as did participants in a collaborative project between the MIND Institute Fragile X Research and Treatment Center at the University of California at Davis, the National Fragile X Foundation, and the Centers for Disease Control

and Prevention (McConkie-Rosell et al. *2007*). Some authors have called for further research to explore potential genetic counseling issues for women ascertained in an infertility setting, including the lack of prior experience with individuals with FXS, the impact of unexpected findings on risk perceptions, regret or anger that testing was not considered earlier in the infertility evaluation process, and the shift of focus to include extended family (McConkie-Rosell et al. *2007*, *2005*; Wittenberger et al. *2007*).

To assess the interest in FMR1 testing among women with a history of ovarian dysfunction (DOR/POF), Pastore et al. (*2006*) surveyed 30 women using a single self-administered anonymous questionnaire. Three factors were most influential for participants who expressed interest in testing: desire to know if they carried the premutation, if their children might potentially carry the premutation, and if the FMR1 gene might explain their history of infertility. The emotional reactions to FMR1 testing among 20 women with DOR were assessed using pre- and post-test questionnaires (Pastore et al. *2008*). While participants in this study projected that learning they carried the premutation would have little impact on how they felt about themselves and their self-esteem, most projected that if they did have the premutation they would feel better knowing there was a medical explanation for their infertility. Among 17 participants without the premutation who completed the posttest survey, most projected that women in their situation who learned they carried the premutation might be angry or regretful for not knowing sooner.

Due to the limited literature on the distribution of FMR1 trinucleotide repeats in women with DOR as opposed to POF, a prospective study that offered this genetic testing in this population was conducted. Within that study, a qualitative sub-study was conducted to further explore the emotional reactions to FMR1 testing among women with DOR and their partners, and this is the focus of this paper. The qualitative study aimed to answer these a priori questions: “What is the experience of undergoing unanticipated genetic testing for fragile X?” and “What is the experience of being the partner of a woman who has been offered this genetic test?” As part of the interviews, these couples spoke of their pregnancy-seeking journey, and therefore this report provides context on their experience of infertility.

Methods

Participants

This was a qualitative, longitudinal study of infertile women ($n = 7$, coded W1–W7) who were undergoing FMR1 genetic testing as part of a research study. Their spouses were also interviewed ($n = 6$ husbands, coded H1–H6). One unmarried female participant was seeking fertility services on her own. The sample size was based on data saturation (Sandelowski *1995*). The source of participants is from a study of the prevalence of fragile X premutations among women with DOR (NIH R03 HD052768). Women were selected based on representing a range of trinucleotide repeats and convenience (East coast time zone). All participants signed informed consents prior to study participation (IRB 11448). Details of the prevalence study are reported

elsewhere (Pastore et al. *2012*). Briefly, all women were diagnosed with DOR based on elevated early follicular phase follicle stimulating hormone (>10 IU/L), regular menses, and age $\leq$ 42 years. Women were excluded if there was a known reason for early ovarian aging (such as chemotherapy) or a family history suggestive of FXS. All participants in this qualitative study resided in North Carolina or Virginia.

Procedures

Three digitally-recorded semi-structured phone interviews were conducted per participant. The initial interview was conducted within 1 week of the study visit, which included a genetic counseling session (LK) and provision of a blood sample. The counseling session (for the female participants only) included an assessment of awareness and prior knowledge about FMR1, information about the study protocol, and discussion of the possibility and implications of detecting a premutation. The second interview occurred within 2 weeks after the genetic test results had been disclosed. The third interview was conducted approximately 3 months later. Each phone interview lasted 20–30 min, and the participants were compensated with $40 for each interview. All interviews were transcribed verbatim, with identifying information removed.

All interviews were conducted by one of three experienced qualitative interviewers. One interviewer (the fifth author) served as the lead interviewer. All interviews for individual study participants were conducted by the same interviewer. The woman and her partner were interviewed separately to reduce any potential bias/constraint in their answers. The interview guide was semi-structured to allow the participant to speak openly about her/his experience of the genetic testing process. Probes were available to the interviewers, but only asked when necessary to encourage participant elaboration. The framework of anticipated narrative content includes variations of probes used in prior research (Anido et al. *2005*). See the Supplement for the interview guide.

Instrumentation

The primary focus of the first interview for female participants was to allow the participant to talk about her experiences since learning she had been diagnosed with DOR and her perspective of fragile X in terms of her reproductive expectations. The primary focus of the first interview for male participants was to gather his reaction to his partner's diagnosis of DOR and to her having this genetic test. The primary focus of the second interview, for male and female partners, was to ascertain their short-term reactions to the actual test result, impact of the test results on reproductive decisions, and any communication with others about the test results or test process. The primary focus of the third interview was to ascertain the longer-term reactions to the test results, and the related communication with others or impact on relationships with others, including the spouse.

Data Analysis

Our qualitative interview philosophy followed the principles of phenomenology. The three major traditions in qualitative research are grounded theory, ethnography and phenomenology. Phenomenology is the tradition concerned with how people go about understanding the world in which they live (Gadamer *1989*; Heidegger*1962*). The phenomenologist will study how people interpret their lives and make meaning of what they experience.

The fundamental purpose of the analysis was to determine the themes that characterize the experiences of the DOR women and their partners in the sample. The process of analysis is similar to processes described by Cohen et al. (*2000*). The transcribed interviews were subjected to standard phenomenological analysis (Cohen et al. *2000*; Kockelmanns *1975*; Steeves and Kahn *1995*), including: overall review of the transcript, rereading transcript to identify "strips" (Agar *1986*) that capture an important aspect of an informant's story, sorting the strips into categories, rereading transcript as a validity check of the categories, and arranging the categories to form themes.

All transcripts from the women were read by an interviewer (the fourth author) and two prenatal genetic counselors (the second and third authors); all the transcripts from the husbands were read by two interviewers (the fourth and fifth authors) and the PI of the study (the first author); one interviewer served on both teams (fourth author). Debriefing occurred within each team (one team for the female transcripts, a second team for the husbands' transcripts) to discuss the data and ensure consistency (Lincoln and Guba *1985*).

Results

Participant Demographics

The seven female participants ranged in ages from 33 to 41 years at Interview 1, with a median of 36 years (Table 1). All participants had FMR1 alleles with CGG repeats less than the premutation range; specifically, their largest FMR1 allele ranged between 27 and 50 repeats. One couple had a child conceived with fertility intervention; otherwise, all other female participants were nulliparous. One husband had offspring from a prior relationship. All female participants were of white non-Hispanic race/ethnicity; corresponding data for the husbands were not ascertained.

Table 1 Participant Summary

Couple ID coding (W = women, H = husband)	**Female age at diagnosis**	**Female age at interview**	**Gravidity (G), parity (P)**
W1, H1	30	36	G1P0
W2, H2	33	34	G0P0
W3, H3	37	38	G1P1
W4, H4	36	36	G0P0
W5, H5	38	38	G1P0
W6, H6	33	33	G2P0

W7	41	41	G0P0

Women's Story

Theme 1: Long Journey

Women in the first interview described their experience of attempting to become pregnant as a long journey. Within this theme, there were three categories: (1) a time-consuming and emotionally exhausting process; (2) feelings of anger or resentment; and (3) feelings of luck or fate.

Category 1: Long Exhausting Process

While one woman had only been seeking fertility treatment for a short period of time (less than 1 year), most had been involved in the process for several years and voiced their frustration over how all-consuming and emotionally taxing the process became: "…did not know that it would be a four-year project that would basically take over my life" (W3). Some women felt that while they were not initially worried that it would take a long time to get pregnant, they also did not want to spend too much time dwelling on the impact the process would have on their life: "You know, we were not in a huge hurry necessarily. So for the first year, it was kind of well, I've been on birth control a long time. I'll just take a while. You know, not to over think type of thing. Will it rule my life?" (W2). Despite the array of medical tests and results that cause detours, they were intent on continuing to pursue fertility treatment: "It's discouraging, but we are moving forward" (W5). Additionally, some women expressed that the lengthy process changed their perspective over time: "Obviously it's been going on so long, I've gone through various stages" (W4) and it had become emotionally exhausting. Not all women felt negatively about their infertility journey. One woman described positive attributes of the process, relating that the energy spent in their infertility journey might have made her more adaptable and better able to process information: "I think better and I don't know if I handle situations better because of how long it took me to get here" (W3).

Category 2: Feelings of Anger and/or Resentment

One woman described infertility as interfering with her life plan: "You get married and have a child [we] just never got to that next step. [I] thought that I was going to have a child" (W4). Still others expressed feelings of resentment and anger in relation to other women who had not had trouble achieving pregnancy: "My sister got pregnant twice with one-night stands the past couple of years. And my mom got pregnant with me and my sister both first try. It was very strange" (W1). "You've got people who (get) themselves into a situation to get gastric by-pass and [it is] something they do to themselves. And we pay for it….and I work with a lot of people [that] for whatever reason seem to have a lot, or seems that a lot of people are having problems with fertility issues and none of them I mean did anything that you know of that would cause it, and insurance won't cover anything"(W7). While most of the women expressed feelings of

frustration and anger, two women considered themselves blessed in other ways: “So when I get sad about our IVF didn’t work, you have to remember, my goodness, this is not cancer” (W1).

Category 3: Luck and Fate

Another significant theme in the initial interview, expressed by all the women in different ways, was the impact of the journey on her sense of luck or fate. “In so many cases it just seems like bad luck” (W3). “You hold your breath every time. Hope you’re a winner, and this month was not my month” (W7). One woman had a unique situation in that she had a child from a previous IVF cycle. She reflected on her feeling of being lucky several times, “You know, it would be ideal if we would have had two children….but we’re so lucky just to have one” (W3). One woman expressed the feeling that with her low chance of getting pregnant, it was difficult to imagine how much they would be willing to go through to get pregnant: “When you are on the small end of the bell curve, you know, it’s a whole different thing to decide you know if this [is] worth it emotionally, financially, physically” (W2). Many of the women expressed a sense of hope for the future, while acknowledging some uncertainty. “Hopefully it’s going to work but I don’t know. I mean, she didn’t say there’s no hope. I mean there was like two or three layers under me so…” (W6). Despite feeling discouraged, they were intent on moving forward.

Theme 2: Hope and Anticipated Impact of Genetic Test Results

Women in this study expressed hope that they were not a carrier of the FMR1 premutation, although to greater or lesser degrees they were starting to consider at the first interview the implications of positive or negative test results from a reproductive and/or fertility diagnosis viewpoint. For example, while most women had a sense of hope about having a negative genetic test result, many acknowledged at the first interview that the test results would potentially have an impact on the direction their infertility journey would take in the future, “If I knew that I was a carrier, I would definitely not use my eggs” (W4). “I wouldn’t want to bring a [child] into this world that might have, you know, a disease that I might pass on” (W7). For many women a positive genetic test result would provide an explanation for their infertility and provide some needed closure. “It might explain why I have not been able to conceive and my sister hasn’t either” (W4). “I will be glad to know what the reason is” (W5). Some women felt that the decision to proceed with testing was an easy decision to make because of their need to have an explanation. “Well, I want to know if I do have fragile X.” (W4). Others, while they wanted to know, were more casual about the decision to have testing stating that, “I don’t have anything to lose” (W6).

Upon first hearing about the possibility of a genetic cause for their infertility, several women were surprised. “Something like that had never crossed my mind before” (W3). The possibility that this was yet another problem that had to be addressed was expressed by several of the women. “When you hear about it, you’re just like, OK do I have that problem” (W6) and “If you

got this, we'll just deal with it" (W1). Many women felt that the decision to test mirrored the process of infertility stating that "I think it's a 1 day at a time thing" (W2).

Theme 3: Relief

Category 1: Relief

All women in our study tested negative for a fragile X mutation or premutation. Thus, at the second interview all women knew their negative test results and the overall feeling expressed was relief. Selected second interview comments on this category are: "very relieved…I think it was floating around in the back of my mind…." (W3) "…if it had been positive then I would consider not going through you know trying to get pregnant anymore…I can keep trying because I know I won't have that" (W6). "…when I got back there was a message here saying that I did not have Fragile X. It was very relieving! ….I think it would have been pretty traumatic if I had been positive" (W4). Note that while they all expressed a sense of relief in finding out that they were not a carrier of the FMR1 premutation, this was in contrast to their feelings during the first interview when the majority stated that they were not particularly concerned about this genetic testing.

Category 2: No Explanation

While the normal genetic results provided a sense of relief, many women also voiced the realization that they may never find an explanation for infertility. Many women had viewed the study as a possible opportunity to uncover an explanation for their DOR/fertility issues. "It still would be nice to know what, what caused all the problems. Um, but we'll probably – I'm guessing we'll probably never know." (W3) "[if it had been positive] I guess it would have given me a reason why I'm not getting pregnant."(W6) "It just sort of ruled out one more sort of potential issue. I guess on the one hand it still means I have completely unexplained ovarian failure, but you know it's not necessarily the reason that you want to hear either." (W2)

One participant's results were in the "intermediate zone" which is above the normal repeat level but below the premutation level. She expressed a feeling of relief but also voiced concerns that perhaps the results that she had might somehow be linked to her infertility.

"So like at first pass it doesn't seem that I have Fragile X so I take that as a good thing… But one of my [alleles] is kind of in this gray zone. So there's still something, kind of an unknown…..And so some things get answered and some things kind of continue on. I feel like I'm in the show *Lost* or something….So it kind of indicates that there's some more mystery behind you know kind of maybe what I'm going through. Maybe they're linked. Maybe they're not linked." (W1)

Category 3: Committed To Prior Journey

Immediately following disclosure of results all women responded that they remained committed to their previously stated family planning strategy. Their plans for a family, and the treatment protocol that they were expecting, had not changed since the first interview. All but one of these women had not yet achieved a successful pregnancy and were planning on future IVF treatments.

All women expressed that a positive test result (i.e., if they had been found to be a carrier of the FMR1 premutation) would have caused them to re-evaluate their future plans regarding IVF treatment. Some participants would have stopped their fertility treatment if they were found to be a carrier. “If it came back that I did have it, I would definitely not [try in-vitro again]” (W1). For others, a positive test result would influence how their IVF process would proceed (i.e.: using donor eggs instead of trying for a biologically related child), as this would confer significant risk for a genetic condition. “If it had been positive…I would have been like ok, well I can’t use my eggs.” (W4)

Theme 4: Change in Plans

At the third interview, women were asked to describe how their fertility treatments were proceeding and what, if anything had changed since the previous interview. The third interviews with the women revealed that, in hindsight, the FMR1 test prompted them to pause and re-evaluate their pregnancy-seeking journey.

More than half the participants altered their reproductive plans since the second interview, three months earlier. In this intervening time period, four out of the seven women had decided to stop fertility treatments, citing physical, emotional or financial exhaustion as their main reason for doing so. “We have actually stopped treatments because number one it was just emotionally exhausting….the last two treatments didn’t work and I was just tired. I mean I was mentally, emotionally, physically, I just couldn’t handle it anymore.” (W6)

In contrast, one woman who was not interested in further IVF in interviews 1 and 2 now was re-considering. W3 who was not interested in pursuing further IVF cycles in the first two interviews decided by the third interview to try for another child and was planning on resuming IVF. “We might give it a try…I think if we would have gotten positive results for that [fragile X test] I wouldn’t consider it now.” Thus, their decision to try again was somewhat linked to the outcome of the genetic testing.

One participant had separated from her husband during the interval between the second and third interview. While this participant acknowledged that there were many factors in her decision to end the relationship, she noted that she and her partner had different feelings regarding the implications of the genetic testing on their pregnancy-seeking journey. She stated that she was being encouraged by her physician to use donor eggs in subsequent IVF cycles. In the third interview she stated “my eggs are still okay” (W4) because her FMR1 premutation test was negative and she hoped that she would have a biologically related child. “But I, I think part of me feels if it had been positive I would have been a lot more amenable to use somebody else’s eggs

cause they basically told me I'd have to use somebody else's eggs if I wanted to proceed with in vitro… I felt like you're asking me to use somebody else's eggs but you're not even wanting to potentially look at using a different sperm, trying that way. *(W4)*"

Men's Story

The following themes were identified from the husbands' interviews, most of which were unique to their perspective, although a few themes paralleled their wives.

Theme 1: Long Journey as a Husband

Category 1: Concern For Wife

The most prominent emotion expressed by the husbands was concern for their wife regarding the fertility treatments, and this emotion was greater than the expressed personal desire for offspring. This husband would have wanted to have the cause of infertility be a male factor, in order to carry the weight of the "cause of infertility": **"**You know I was almost hoping that the problem was with me. You know you only need one good strong little swimmer to get in there and I thought it would be easier to overcome problems with me than with her." (H3, interview 1) This husband expressed the toll he sees on his wife from the diagnostic test results: **"**You know, the emotional, the physical roller coaster she's had hope by hope by hope, and then when you go in and you know the doctor sits there and says for the medical, you know for the checkup prior to going in, seeing how many eggs you have and there's nothing there. I mean sometimes you can't put a value on the emotional toll that it actually takes on her." (H2, interview 1)

When there was additionally a male factor underlying the fertility challenges, it was a relief to have a shared role. "It came back and you know we were told that she did have uh Diminished Ovarian Reserve. And then when my results came back we found out that you know I was um, I guess on the low end of the scale as far as… it was almost a relief that, you know, we were in this together." (H1, interview 1) The husbands felt sympathy for their wives regarding the fertility treatment itself, as the treatment generally required her to take pills and/or receive injections. "I feel for her. She obviously um had to bear a much bigger um burden as far as the physical, um kind of thing - and um plus the shots you know, the procedures, etc." (H1, interview 1)

In terms of the decision-making regarding fertility treatment, the men expressed the feeling that they were less consumed with the process and were more likely to be passive participants, following the lead of their wives. "I've been on the sidelines watching." (H3, interview 1) "I mean it's kind of in the back of her mind I know a lot more than, than mine. Just because you know I think she thinks about it really a lot more." (H6, interview 3) It should be noted that the women consistently used "we" to describe their reproductive decision-making process, though one woman remarked "I'd like to have a general opinion [on adoption] before I really begin to convince HUSBAND because he'll - I'm sure I can get him to go along with what I feel" (W1).

Category 2: Frustration Expressed As Financial Remarks

The expense of the fertility treatments were mentioned by nearly every male participant, and this was a consistent topic through which the husbands expressed frustration**.** "You know I hate to correlate a child to the uh…some things, but it's basically the cost of a car." (H3, interview 1) "It's like 15 grand for one procedure. But if you spend 25 grand or 30 grand you get four procedures and it's guaranteed to give you a kid or you get your money back. I mean my guess if you went through four procedures and didn't have a kid the $30,000 would barely pay for your divorce." (H5, interview 1) "And I guess that's my frustration in this whole thing is you know here we are spending all this money and it's not cheap by the way. It's very expensive going through this whole procedure. We're already in twenty grand and we're not done and that's the hard pill to swallow … here we are spending our money and we have no tangible outcome and no one is able to guarantee that we will get something." (H2, interview 1)

Theme 2: Quest for Knowledge

Category 1: Surprise

In terms of having the FMR1 genetic test through the research study, the husbands were surprised to be offered a new genetic test after the length of time spent in fertility treatment. "Now here's another uh, you know, condition that neither of us had I think knew anything about prior to, prior to participating in the, in the study." (H1) This was a concept that was also expressed by two of the wives: "I did not even know about the Fragile X, so it was really something that was discovered with the study." (W6)

A minority of the husbands initially viewed the genetic test as potentially impacting their future reproductive decisions: "I don't think it, it you know would stop us in our tracks if she comes back with a positive result." (H3) However, it was more common for the men to view the genetic test as a potential explanation for the DOR diagnosis or as a decision criterion on whether IVF would be successful or not, as opposed to focusing on the potential reproductive implications (i.e., having a FXS offspring) from carrying the FMR1 premutation. "I guess we're using this and other things to make sure with our doctor that you know … in vitro … would we be good candidates for that." (H6)

Category 2: Self-Reliance

The partners researched fertility topics to answer their own questions and/or to answer questions on behalf of their wives. They definitely expressed a self-reliance to be able to research Fragile X and to be able to interpret the results for themselves. "Yeah, that's why I have to educate myself some more. … Yeah, you know I have to do some research on this, too." (H3) "I just don't know enough about what it would mean and… I would want a lot more information…before I could make sort of an informed decision. …I'm going right to the uh Wikipedia, that's my source information I'm sure. Or… who knows the power of the internet."

(H1) Some men seemed to take a "wait and see" attitude as opposed to having a plan of action depending on the genetic test results: "I haven't done enough research yet to, I guess to understand how much stock I should put into if it comes back positive." "I just don't know enough about what it would mean and… I would want a lot more information…before I could make sort of an informed decision." (H1) Often they gathered only enough information in response to the immediate need, as expressed by this husband at the second interview: "… just didn't want to extend a lot of emotional energy that we have around that if it might not be the case." (H1) Only one husband referred to working with the fertility clinic to interpret the results: "Well, I generally like to start with you know the doctor. Her help and then any information that she gives us. And we ask her when we're there you know if there're any other you know web sites that she'd recommend or any type literature and things like that." (H6)

Category 3: Drive for Information

The husbands were very information-driven, and this was one distinguishing difference with the interviews of the women. They commented on the lack of definitive, trustworthy sources from which they could research fertility matters and the volume of information on the web, albeit not always factual information. "So when you go online and you start researching you have all of these forms that aren't maintained by a medical professional and they're by people who are actually just going through their experience. So it's just – there's so much information out there that it's hard to get a true idea of you know who should I talk to?" (H2, interview 1) "You know we're not sure of the validity of the information and it can be a little bit of an overload, which probably wouldn't – definitely wouldn't help the situation any." (H6, interview 1)

The men did not have any idea what their reproductive future held, and they related this uncertainty to a lack of information. They described their infertility situation and reproductive future as a puzzle. "It's already a jig saw puzzle. We're putting it together as best we can without any instructions you know. … there's just too many potential possibilities of those issues that could be wrong and there's no way to narrow down what exactly the root cause." (H2, interview 1)

Theme 3: Reaction to the Genetic Test Results

Category 1: No Explanation

As mentioned previously, none of the women in this qualitative study carried the FMR1 premutation. In the short term (interview 2), for some men, the negative genetic results were interpreted as "there is no further info on the reason for the infertility". This was <u>not</u> expressed as an emotional disappointment, but rather as another fact or puzzle piece. "If we would have found out that's what she had [i.e., carried the FMR1premutation] we would have said, fine, all right let's move forward. Let's use somebody else's eggs, blah, blah. But now she's like I don't know what it is and there might be a chance I can't you know and how long and how many thousands of dollars?" (H4) In contrast, one husband did not anticipate that the genetic test

result would have impacted their reproductive decisions had it been positive for a premutation. This husband, at Interview 2 after learning the negative test result, implied that he wished for a pregnancy whether or not she carried the FMR1 premutation.

“And I think we would be thrilled to be just having that worry at this point. I mean and going through those different scenarios. … Knowing what I, the little bit that I know, I don’t know that that thought at this particular thing would have affected our decision to move forward or not.” (H1)

Category 2: Relief Immediately Following the Test Results (Interview 2)

Only one husband expressed relief at the negative FMR1 test results. “If I had known the details of the implication of the positive result it may have been stronger. But even based on what I did know it was certainly a relief.” (H3) Thus by the lack of such comments, this suggests that most husbands assimilated the test results as “more information” rather than viewing the FMR1 test results with a test-specific emotional reaction.

Three months after the test results were communicated, the husbands looked back on the genetic testing experience as a fork in the road, similar to their wives. In hindsight (interview 3), husbands looked back at the testing and voiced relief at their spouse’s not carrying the premutation and therefore not having the risk of a FXS offspring:

“And you know the plans weren’t really set in place before you know. We weren’t a 100 percent certain that we wanted to try you know for another child. Um but if the tests had come to back to where you know that the child would be at a significantly higher risk, it would have weighed pretty heavily on our decision whether to proceed or not. I think the Fragile X testing probably put the subject at the forefront for discussion as opposed to it being you know kind of a passive discussion about you know whether to proceed to expand the family or not.” (H3)

Discussion

Summary of Findings and Comparison to the Literature

The goal of this study was to explore the experiences of infertile women, and their partners, to unanticipated genetic testing, specifically FMR1 testing. All women in this study were diagnosed with DOR, and understood the reproductive impact of a positive test result when presented with an opportunity for FMR1 genetic testing. They hoped for a negative test result, experienced relief when the result showed they were not carrying the premutation, and would have reconsidered their reproductive plans if test results had found them to have the premutation. The husbands of these women viewed the FMR1 genetic testing primarily as a potential explanation for their wife’s DOR diagnosis, perceived the test result as another fact in the “puzzle” of their reproductive journey, and were willing to not have all the facts about this gene prior to receiving the results. For both the women and their husbands, the test result, in hindsight, was a fork in the

road because a positive premutation result would have influenced their reproductive decision making.

Separate from the genetic testing process, women reported that their pursuit of pregnancy was long and exhausting. Feelings of anger and resentment, as well as a sense of luck or fate were expressed. These responses are supported by other qualitative studies of women who had pursued fertility-related medical treatment, specifically the physical and emotional impact of fertility tests and treatment (Imeson and McMurray *1996*), resentment and dealing with ongoing fertility delays (Glover et al. *2009*), hope and loss at the same time (McCarthy *2008*), and frustration and anger (Whiteford and Gonzalez *1995*). Our female participants reflected a similar perspective to another study of women with a diagnosis of DOR (Friese et al.*2006*), where women perceived the DOR diagnosis as a "rude awakening" and expressed a sense of lost or wasted time.

Anido et al. (*2005*) conducted focus groups of women from the general population who had agreed to FMR1testing (via saliva samples collected outside of a medical setting) and did not carry the premutation. The motivations for testing in our sample were similar to the women in the Anido et al. study who had children (that is, they were interested in the results for family planning purposes), but not the Anido subset without children (who perceived the motivation to test as similar to getting a cholesterol test or to benefit research). Both our sample and the Anido sample "expressed that positive premutation results could have led to their reconsidering life plans especially their decision to have children" (Anido et al. *2005*, p. 301).

In general, the husbands in our study expressed concern for their spouse relative to the diagnosis and the fertility treatments. The men tended to be passive participants in the fertility journey, and were focused on gathering data, both relative to the fertility diagnosis/treatment and to the genetic testing. These sentiments are generally supported by prior literature suggesting men engage in data gathering as a means to have some control (Wilkes et al. *2009*), and they focus on their partner's experience rather than their own experience (Sherrod *2006*). Kenen et al. (*2000*) interviewed couples regarding prenatal genetic testing (e.g., amniocentesis and chorionic villus sampling) and found the male partners viewed that testing as either an "information" decision (defined as a precursor to having to make a "real" decision) versus an "active" decision (e.g., viewing the decision to have an amniocentesis test as a decision to assume the risk of that procedure). Using their framework, the husbands in our study viewed the FMR1 testing as an "information" decision. This perspective was very evident in the numerous ways the husbands referenced the genetic test result as another puzzle piece and part of data gathering in the quest for a biological child.

As reviewed by Greil and colleagues (Greil et al. *2010*), men and women are affected differently by infertility, and our observations reflect differences in the key themes expressed by women and their husbands. In common to both partners was verbalization of the financial burden of medical

fertility treatments, as has been reported previously (Nachtigall et al. *2012*), though this was voiced more strongly by the husbands.

Unanticipated Genetic Testing

Infertile women seek fertility assistance because they want to become pregnant, and are unlikely to have any reason to think their infertility is related to a genetic condition. They often have undergone months and years of unsuccessful fertility treatments and tests (see theme 1 category 1), and may consider FMR1 testing to be at long last an explanation for their conception difficulties (theme 2). Women with a diagnosis of DOR have lower success rates with assisted reproductive technologies regardless of age (Akande et al.*2002*; Yanushpolsky et al. *2003*). The inability to become pregnant with conventional treatment can result in "the feeling that they have lost control over an important and very personal part of their lives" (Speroff and Fritz *2005*) (p 1,022). Couples may or may not want to consider alternatives, such as donor oocytes or adoption. So these DOR women may also be experiencing some anticipatory grieving, given the unlikely prospect of having a baby conceived with their ovum. Thus, the patient enters the genetic testing process in a complex emotional state, and without anticipation that her genes may be a key factor underlying her infertility.

Specifically regarding FMR1 testing in a fertility clinic setting, we sought to determine whether these women perceived the decision to be tested as different from other non-genetic test decisions. Our results suggest that infertile women and their spouses viewed FMR1 testing as another step in the process of infertility evaluation and management.

In a recent commentary about population screening for genetic conditions including FXS, Archibald and McClaren (*2012*) noted that initial judgments about the relevance of testing were centered on two key areas: reproductive state of life and health-related experiences. The desire to know if their conception difficulties might be due to this gene contributed to interest in FMR1 testing among women with DOR and POF in a prior study (Pastore et al. *2006*). Consistent with these observations, although participants in this study expressed surprise at being offered genetic testing, they recognized the medical importance of FMR1 testing for their future fertility planning. Participants expressed satisfaction with the testing process, and did not express any difficulties in making decisions about testing.

In addition to being experienced as a turning point where their previously stated reproductive decisions could be altered, women viewed the process of being offered a genetic test as a symbolic break point. This event precipitated a pause in their infertility pregnancy–seeking journey, where they reconsidered their goals and motivations regarding fertility treatment.

Anticipated Impact of Genetic Test Results on Family Planning Decisions

While expressing a sense of hope about not carrying the FMR1 premutation, the women, and their spouses viewed finally having a medical explanation for their infertility as a potential

benefit of FMR1 testing. Thus, both women and their spouses expressed relief *and* disappointment regarding the negative test results. These findings are consistent with those of a previous study (Pastore et al. *2008*) in which women with DOR were surveyed before and after FMR1 testing. In that study most participants projected that if they carried the FMR1 premutation they would feel better knowing that there was a medical explanation for their infertility; about half of the participants projected that they would be less likely to have a biological child. Reproductive decision-making is a multi-factorial process for all couples who plan a pregnancy. The inclusion of a potential inherited condition into the equation magnifies the complexity of the process, as well-documented in research on reproductive choices among couples who had been screened for Huntington's Disease (Decruyenaere et al. *1996*, *2007*).

Implications for Genetic Counseling Practice

All participants in this study received genetic counseling prior to FMR1 testing. Recommendations on the content of pre-FMR1-testing genetic counseling sessions have been published (Finucane et al. *2012*; McConkie-Rosell et al. *2005*). This genetic counseling session may account for the participants' ability to understand both the potential implications of positive results on future reproductive planning as well as the implications of negative test results. Outside of a research setting, FMR1 testing may be offered to women with POI without the benefit of pre-test genetic counseling. While specialists in reproductive medicine can provide a supportive environment to explain the meaning and implications of FMR1 testing (Wittenberger et al. *2007*), it is important that patients with POI have access to tailored educational materials and consultation with genetic counselors before and after testing as needed. Additional research focused on the counseling and educational needs of women with POI with regards to FMR1 testing is needed, especially as research may continue to uncover associations between POI and high normal (Pastore et al. *2012*; Streuli et al. *2009*) or intermediate (Gleicher et al. *2009*; Karimov et al. *2011*) level trinucleotide repeats (35–44 and 45–54 CGG repeats, respectively).

Study Limitations and Strengths

Qualitative data are not intended to be generalized to the population of interest. Therefore, conclusions based on the present findings should be made with caution. The generalizability of our findings also is limited to women and men seeking medical intervention to enhance fertility, and may be further limited to women willing to participate in a study and willing to have a genetic test. The uptake rate of FMR1 newborn screening was 63 % in a pilot study, and varied by race-ethnicity (Skinner et al. *2011*). The participants in the present study all agreed to partake in a genetic research study, and thus, the context of the FMR1testing is different than the clinical setting. All female participants in the study were non-Hispanic white, which reflects the majority of patients treated for infertility in the US (Bitler and Schmidt *2006*); as reported elsewhere, there are race, ethnic and educational disparities in access to fertility treatment even in states with mandated insurance coverage for fertility treatment (Bitler and Schmidt *2006*). The women

who participated in this study had all tested negative for FMR1 premutations. The initial reactions to being offered FMR1 testing and the anticipated impact of genetic test results on family planning decisions may or may not be similar in women who test positive; additional research to describe the short and long-term reactions to testing among women who test positive is needed.

A strength of this report is that it adds to the scarce body of qualitative research on FMR1 genetic testing in women without a family history of Fragile X Syndrome. Additionally, there is limited qualitative research on reproductive decision-making in partners of individuals undergoing testing for inherited or other genetic conditions; examples of such research outside of FMR1 testing are cited (Decruyenaere et al. *2005*; Kenen et al. *2000*).

Research Recommendations

As all participants in this study did not carry the FMR1 premutation, a continuing gap in the literature is the short-term and longer term impact on reproductive decision-making in those with the premutation (and their partners) who do not have a family history of FXS. As mentioned previously, continued research on genetic counseling and educational needs of women with POI with regards to FMR1 testing is needed. FMR1 genetic counseling is complex due to the range of potential phenotypes, the incomplete penetrance of a phenotype even with full mutations, and the evolving scientific knowledge of the human health impact from the FMR1 gene.

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Electronic supplementary material

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