CHAPTER

7

Women's Issues in Fragile X Spectrum Disorders

Jessica Ezzell Hunter, Anne C Wheeler, Emily Graves Allen, Kaitlyn Wald, Aleksandar Rajkovic, Randi J Hagerman, and Stephanie L Sherman

WOMEN'S ISSUES IN FRAGILE X SPECTRUM DISORDERS

Mothers and grandmothers of children with fragile X syndrome (FXS) are confronted with many issues that impact their children, their own health, and the extended family's health. Raising a child with FXS can be very stressful and the fragile X premutation influences the body's response to stress. Women with a premutation are at risk for unique health conditions that are not associated with carrying a full mutation. They have a high risk for fragile X-associated primary ovarian insufficiency (FXPOI) and a variety of health problems including thyroid disease, fibromyalgia, chronic fatigue, hypertension, anxiety, and depression. In addition, genetic counseling will lay out the options of future reproduction and in vitro fertilization (IVF) in a way to ensure a desired pregnancy. Hormonal replacement therapy and the diagnosis of FXPOI will be reviewed in detail. Various interventions to stay healthy in aging will be reviewed.

MATERNAL STRESS AND STRESS CORRELATES

Caring for a child with intellectual and developmental disabilities (IDD), such as FXS, can lead to higher levels of maternal stress compared to those experienced by mothers of typically developing children due to the unique psychosocial, financial, and physical challenges (Abbeduto et al. 2004; Bailey et al. 2008b; Smith et al. 2010). Elevated maternal stress can lead to maladaptive outcomes, such as decreased maternal quality of life, elevated rates of depression and anxiety, and impaired social functioning (Sarimski 1997; Franke et al. 1998; Rodriguez-Revenga et al. 2008; Bailey et al. 2008b; Roberts et al. 2009; Lovell et al. 2012). Thus, recent research focused on premutation (PM)-associated outcomes, such as increased rates of mental health issues, has aimed to discern the dual contributions of the genetic vulnerability inherent to carrying a PM allele and exposure to elevated maternal stress.

Prior studies have indicated that the biggest predictor of maternal well-being and caregiver burden among mothers of children with FXS is related to child behavior problems (Bailey et al. 2008b; Bailey et al. 2012). Specifically, results from a national parent survey indicate that child behavior problems significantly contributed to parental stress, symptoms of depression and anxiety, and quality of life (Seltzer et al. 2010). Blunted cortisol responses have been reported among mothers of children with IDD, with

severity of child behavior the day before predicting cortisol responsivity, indicating a dysregulation of the neuroendocrine response to maternal stress. The presence of non-maternal stress (e.g. work stress) has also been found to predict cortisol awakening responses among mothers of children with FXS or autism spectrum disorder (ASD), but not among mothers of children without an intellectual or developmental disability (Wong et al. 2014). These results indicate that women experiencing elevated maternal stress are at risk of altered cortisol reactivity and are more susceptible to the impact of stress in general.

However, some studies indicate a genetic vulnerability to stress conferred by carrying a PM. Hartley et al. (2012) reported that women with a lower X inactivation ratio (i.e. a lower percentage of cells with the normal X chromosome active compared to the X chromosome with the PM allele) had lower levels of cortisol on mornings following days when their child manifested more episodes of behavior problems compared to mothers with higher X inactivation ratios. Seltzer et al. (2012) reported higher rates of anxiety and depression and a more blunted cortisol awakening response in mothers of a child with FXS who had experienced a stressful life event the year before, with women carrying premutation alleles in the mid-range being the most at risk compared to those with higher or lower-sized PM repeats. This unusual non-linear association with repeat size has also been found with FXPOI (Sullivan et al. 2005; Allen et al. 2007).

Hunter et al. (2012) reported among mothers of children with FXS a subset was at increased risk of social anxiety with this risk based on the genotype for a major regulator of cortisol reactivity, corticotrophin releasing hormone receptor 1 (CRHR1). These results indicate an impact of genetic variability on cortisol reactivity beyond carrying a PM. These findings were significant as an increased risk of social anxiety may limit a woman's ability to seek help and establish robust social support systems, two factors important to the mental health outcomes of mothers of children with FXS (Bourke-Taylor et al. 2012).

Altogether, these findings indicate that women with a PM may be more susceptible to dysregulation of cortisol response in response to stress and that mental health outcomes among women who carry a PM allele may be attributed to or exacerbated by the psychosocial impact of raising a child with FXS. These findings are consistent with the diathesis–stress model, which aims to explain the impact of stress exposure on mental health by attributing variability to resilience to stress as a result of genetic or developmental factors (diathesis) in conjunction with exposure to stressful events that bring about the onset of a mental health disorder (Feder et al. 2009). However, there is much to be understood about the relationship between carrying a PM, stress, stress-associated biological pathways, and mental health outcomes among women with a PM.

Recent evidence indicates that mindfulness and acceptance play a protective role in parenting, and are associated with reduced stress, anxiety, depression, and daily health symptoms among mothers of children with FXS (Wheeler et al. 2018). In addition, a recent study reported the feasibility of a smart phone app for mindfulness training among mothers of children with FXS, suggesting an accessible tool for improving mindfulness and the health and well-being of women experiencing elevated stress (Hunter et al. 2019).

FXPOI

Roughly 20% of women who carry a PM develop fragile X-associated primary ovarian insufficiency (FXPOI) over their reproductive lifetime compared to 1% in the general population. In fact, the fragile X PM is the most common single gene cause of primary ovarian insufficiency (POI) (Sherman 2000). POI is a spectrum and is diagnosed when indicators of ovarian function are reduced and show an impaired response, although women may still be having menstrual cycles (Welt 2008).

FXPOI is diagnosed based on the presence of (1) unpredictable (more frequent or skipped menses) or absent menses for 4 months before age 40, and (2) menopausal levels of serum follicle stimulating hormone (FSH), on two occasions 1 month apart. Women with FXPOI may experience symptoms of estrogen deficiency, such as hot flashes/flushes, night sweats, vaginal dryness and painful intercourse. Reduced levels of anti-Mullerian hormone (AMH) may indicate decreased ovarian reserve (or impaired ovarian responsiveness) in earlier stages of POI and may be useful for screening (Rohr et al. 2008; Spath et al. 2011). Low AMH, however, is not diagnostic of POI since women can continue to have regular cycles for years with an undetectable AMH. It should not be assumed that irregular menses are due to FXPOI even if a woman is known to carry a PM. Initial diagnostic investigations should include a pregnancy test, measurement of serum FSH, prolactin, and thyroid hormone levels to assess for other medical conditions, such as thyroid disease, polycystic ovarian syndrome, or pregnancy, which can present similarly.

In the past, both premature ovarian failure (POF) and premature menopause were used to describe POI; however, these are not as accurate, as there are differences between menopause and POI besides the age of the woman. About 50% of women diagnosed with POI have varying and unpredictable ovarian function. Indeed, about 5–10% of women with POI go on to conceive a viable pregnancy following their diagnosis of POI (Taylor et al. 1996; van Kasteren and Schoemaker 1999; Rebar 2009). This rate may be higher among women with FXPOI (about 13%), as indicated in a recent study (Hipp et al. 2016).

Importantly, there are many women with a PM who go through natural menopause at a similar age to women without a PM. This variability emphasizes the importance of identifying risk factors to predict onset of FXPOI. Women who carry a PM should inform their primary care physician or gynecologist of their increased risk for POI in order to facilitate recognition of early symptoms and better management. All women presenting with POI should be tested for the fragile X PM, regardless of their family history (American College of Obstetricians and Gynecologists 2017). The National Fragile X Foundation has provided a consensus document for FXPOI written by the Fragile X Clinical and Research Consortium from which much of the following information was drawn (see www.fragilex.org).

Currently, there is no treatment to regain ovarian function for women with FXPOI. However, there are ways to address the clinical and emotional consequences associated with POI (Nelson 2009):

1. **Emotional well-being.** The loss of fertility due to POI can be emotionally devastating. Healthcare providers should be prepared to address the psychological impact of this diagnosis and provide appropriate support and resources. Furthermore, women with the PM may be at increased risk for depression and anxiety; thus, a follow-up visit to screen for symptoms of depression and anxiety is suggested.
2. **Hormone replacement therapy (HRT).** The American Society for Reproductive Medicine and the International Menopause Society recommend hormone replacement therapy (HRT) for women with POI (Board of the International Menopause Society et al. 2007; Practice Committee of the American Society for Reproductive Medicine 2004) to promote bone density growth. Importantly, the conclusions of the Women's Health Initiative (Rossouw et al. 2002) conducted on older women do not apply to young women with POI given bone density growth continues through the 20s and 30s. There is an age window during which HRT is beneficial, and its use is recommended by The North American Menopause Society until the median age of natural menopause (North American Menopause Society 2012). However, a recent study indicated that, less than half of the women with FXPOI receive optimal HRT use, with the majority reporting that their doctor never mentioned HRT use or even advised against using HRT (Hipp et al. 2016). Thus, there needs to

be increased awareness of the benefits of HRT for women with FXPOI. In interviews with women carrying a PM, Hipp et al. (2016) revealed that a proportion of women, and in some cases their physicians, did not appreciate the importance of HRT in young women with POI. Thus, each woman should openly voice her questions or concerns about HRT and discuss alternatives and risks with her physician to identify her best option for care. At the age of 50, the risks and benefits of HRT should be reevaluated.

3. **Bone mineral density.** Estrogen deficiency resulting from POI leads to reduced bone mineral density and osteoporosis. Bone mineral density should be measured at the time of diagnosis of POI, with follow-up depending on the result. Women with FXPOI are recommended to follow general guidelines to minimize bone loss. This includes weight-bearing physical activity and a healthy balanced diet. Calcium intake is recommended, though calcium obtained through food is preferred over supplements given the additional nutritional value of dairy products. The recommended dietary allowance (RDA) for calcium is 1000mg per day for women 19–50 years old and 1300mg per day for girls 9–18 years old. Adequate vitamin D status is recommended, indicated by a serum 25-hydroxyvitamin D level of 30ng/ml (75nmol/L). Supplementation may be required based on lifestyle. Bisphosphonates are not recommended in young women with POI because of potential embryo toxic effects in the event of a subsequent unexpected pregnancy (Nelson 2009). On the appropriate regimen of physiologic HRT up to the typical age at menopause (~50 years of age), bone mineral density can return to normal in women with POI, although this has not been tested in women with FXPOI. Recommendations for women older than 50 years should be assessed by each woman's clinician.
4. **Family planning.** Women with FXPOI should assume that they can get pregnant spontaneously, as noted above. Contraception is recommended for those not wanting to conceive. For all women, intra-uterine devices are recommended over oral contraceptives, but each woman should make their decisions based on the advice of their clinician and their own lifestyle. A menstrual diary is advised, with prompt pregnancy testing in the case of late menses.
5. **Parenthood.** There are several reproductive options available to women with FXPOI, all of which should be discussed with a woman diagnosed with FXPOI. Some women may choose to not intervene and see if conception happens naturally while on HRT. Some women may choose fertility treatment, such as IVF. This option allows for preimplantation genetic testing (PGT) to test for a fragile X mutation. Fertility treatment with a woman's own eggs may not be successful depending on the severity of diminished ovarian reserve. In cases of severe diminished ovarian reserve, a woman may not be considered a candidate to try IVF. Some women choose adoption. Some women proceed with other assisted reproductive technologies using egg or embryo donation.

Women with a PM who have mild FXPOI or are at risk for FXPOI, but are not yet ready for family planning, may consider oocyte or embryo cryopreservation. This approach allows women to wait until they feel ready to conceive.

In general, women diagnosed with FXPOI who desire pregnancy should not take the oral contraceptive pill because it is known to create hostile cervical mucus, which impedes the ability of sperm to reach the egg should they ovulate. Also, the oral contraceptive pill is known to cause thinning in the lining of the uterus, which may impede implantation of the embryo should an egg be fertilized. Physiologic HRT has the advantage of lowering serum luteinizing hormone levels to normal in women with FXPOI, which theoretically could improve their chance of typical follicle growth and subsequent ovulation. When a woman is diagnosed with FXPOI, a referral to a genetic counselor is very helpful to discuss the risks of transmission of the fragile X pre or full mutation to offspring and the risk of fragile X-related conditions in other family members.

PM WOMEN AND OTHER CLINICAL OUTCOMES

Following the description of FXPOI in premutation women in 1999 (Sherman 2000), medical comorbidities related to FXPOI, such as osteoporosis, were identified (Hundscheid et al. 2003; Allen et al. 2007). More recently, a broader spectrum of disorders among all women carrying a PM has been reported. In 2008, Coffey et al. (2008) reported a significant increase in many medical comorbidities in a study of 146 premutation carriers and 69 non-carriers. Women with a premutation showed a significant increase in reporting of thyroid problems, hypertension, seizures, fibromyalgia, muscle pain, and symptoms related to fragile X-associated tremor/ataxia disorder (FXTAS) such as tremor, ataxia, and neuropathy. This study sample was expanded by Winarni et al. (2012) with 344 PM carriers and 72 control women. A comparison of groups revealed a significant increase in immune-mediated disorders, autoimmune-type thyroid disorders, and fibromyalgia among women with a premutation. A national parent survey that included results on 199 premutation females found an increase in reporting for anxiety (31%), depression (28%), and attention problems (14%) and these individuals did not have children with FXS (Bailey et al. 2008a). An additional study by Hunter et al. (2010) reported a significant increase in mental health disorders (attention deficit hyperactivity disorder [ADHD], anxiety, and depression) and learning disabilities among 334 PM carriers compared with 203 non-carriers. Survey data from Wheeler and colleagues found that women with a diagnosis of FXPOI were also more likely to experience dizziness, nausea, and muscle weakness compared to women without a diagnosis of FXPOI. Also, they found that having comorbid depression and anxiety was predictive of increased medical conditions and increased daily physical health symptoms (Wheeler et al. 2014). A recent study performed an unbiased population-based review of electronic medical records and found increased health service use, diagnoses, and greater burden of disease among younger adults with the PM than controls (Movaghar et al. 2019).

The molecular cause of these varied conditions is currently unknown. A study on the metabolomics of 23 premutation carriers, both men and women, compared to 16 controls did identify metabolites that have been associated with depression, learning and memory deficits, increased inflammation, anxiety-related disorders, mood disorders, and mitochondrial dysfunction (Giulivi et al. 2016). In a review of the many co-occurring conditions in premutation carriers, Hagerman et al. (2018) recently termed the large group of neuropsychiatric problems of premutation disorders FXAND: fragile X-associated neuropsychiatric disorders. The variety of neuropsychiatric disorders under this umbrella term includes depression, anxiety, chronic fatigue, chronic pain, ADHD, obsessive compulsive disorder, ASD, and sleep disturbances (Schneider et al. 2016; Hagerman et al. 2018). Since some of the FXAND conditions are more common in carriers compared to FXPOI or FXTAS this term was created so that clinicians and researchers are more aware of these problems and focus on the need for treatment.

The most common of the FXAND problems, depression and anxiety, typically respond well to selective serotonin reuptake inhibitors (SSRIs) and counseling even when they occur in childhood. Stimulant medication works well in the treatment of ADHD, particularly in childhood, but sometimes these medications are needed in adulthood too. These problems associated with the premutation are likely related to the calcium dysregulation leading to mitochondrial dysfunction and oxidative stress. Therefore exercise, which can improve the psychiatric problems and the mitochondrial dysfunction, can be helpful and is recommended on a daily basis (Polussa et al. 2014). In addition, antioxidants such as green tea, fresh berries, omega 3, curcumin, and other supplements are recommended to counteract oxidative stress (Polussa et al. 2014).

FXTAS occurs in only approximately 13–16% of women with the premutation and when this occurs it is typically more mild than the symptoms that are seen in males (Hagerman and Hagerman

2016). Women rarely demonstrate the classic sign of white matter disease in FXTAS seen on MRI called the middle cerebellar peduncle (MCP) sign, seen in 60% of males with FXTAS. The symptoms of FXTAS and treatment issues in males and females are described in more detail in Chapter 8.

ACKNOWLEDGEMENTS

Dr Hunter would like to acknowledge funding from the Kaiser Permanente Community Benefit Initiative. Dr Hagerman would like to acknowledge funding from NICHD HD036071 and the MIND Institute IDDRC U54 HD079125. Drs Sherman and Allen would like to acknowledge funding from U54NS091859.

REFERENCES

American College of Obstetricians and Gynecologists (2010) ACOG Committee Opinion No. 469: Carrier screening for fragile X syndrome. *Obstet Gynecol* **116**: 1008–1010.

American College of Obstetricians and Gynecologists (2017) Carrier screening for genetic conditions. Committee Opinion No. 691. *Obstet Gynecol* **129**: e41–55.

Abbeduto L, Seltzer MM, Shattuck P, Krauss MW, Orsmond G, Murphy MM (2004) Psychological well-being and coping in mothers of youths with autism, Down syndrome, or fragile X syndrome. *Am J Ment Retard* **109**: 237–254.

Allen EG, Sullivan AK, Marcus M et al. (2007) Examination of reproductive aging milestones among women who carry the FMR1 premutation. *Hum Reprod* **22**: 2142–2152.

Bailey Jr DB, Raspa M, Bishop E et al. (2012) Health and economic consequences of fragile X syndrome for caregivers. *J Dev Behav Pediatr* **33**: 705–712.

Bailey Jr DB, Raspa M, Olmsted M, Holiday DB (2008a) Co-occurring conditions associated with FMR1 gene variations: findings from a national parent survey. *Am J Med Genet A,* **146a**: 2060–2069.

Bailey Jr DB, Sideris J, Roberts J, Hatton D (2008b) Child and genetic variables associated with maternal adaptation to fragile X syndrome: a multidimensional analysis. *Am J Med Genet A* **146a**: 720–729.

Board of the International Menopause Society, Pines A, Sturdee DW et al. (2007) IMS updated recommendations on postmenopausal hormone therapy. *Climacteric* **10**: 181–194.

Bourke-Taylor H, Pallant JF, Law M, Howie L (2012) Predicting mental health among mothers of school-aged children with developmental disabilities: the relative contribution of child, maternal and environmental factors. *Res Dev Disabil* **33**: 1732–1740.

Coffey SM, Cook K, Tartaglia N et al. (2008) Expanded clinical phenotype of women with the FMR1 premutation. *Am J Med Genet A* **146a**: 1009–1016.

Feder A, Nestler EJ, Charney DS (2009) Psychobiology and molecular genetics of resilience. *Nat Rev Neurosci* **10**: 446–457.

Franke P, Leboyer M, Gansicke M et al. (1998) Genotype-phenotype relationship in female carriers of the premutation and full mutation of FMR-1. *Psychiatry Res* **80**: 113–127.

Giulivi C, Napoli E, Tassone F, Halmai J, Hagerman R (2016) Plasma metabolic profile delineates roles for neurodegeneration, pro-inflammatory damage and mitochondrial dysfunction in the FMR1 premutation. *Biochem J* **473**: 3871–3888.

Hagerman RJ, Hagerman P (2016) Fragile X-associated tremor/ataxia syndrome – features, mechanisms and management. *Nat Rev Neurol* **12**: 403–412.

Hagerman RJ, Protic D, Rajaratnam A, Salcedo-Arellano MJ, Aydin EY, Schneider A (2018) Fragile X-associated neuropsychiatric disorders (FXAND). *Front Psychiatry* **9**: 564.

Hartley SL, Seltzer MM, Hong J et al. (2012) Cortisol response to behavior problems in FMR1 premutation mothers of adolescents and adults with fragile X syndrome: a diathesis-stress model. *Int J Behav Dev* **36**: 53–61.

Hipp HS, Charen KH, Spencer JB, Allen EG, Sherman SL (2016) Reproductive and gynecologic care of women with fragile X primary ovarian insufficiency (FXPOI). *Menopause* **23**: 993–999.

Hundscheid RD, Smits AP, Thomas CM, Kiemeney LA, Braat DD (2003) Female carriers of fragile X premutations have no increased risk for additional diseases other than premature ovarian failure. *Am J Med Genet A* **117a**: 6–9.

Hunter JE, Jenkins CL, Grim V et al. (2019) Feasibility of an app-based mindfulness intervention among women with an FMR1 premutation experiencing maternal stress. *Res Dev Disabil* **89**: 76–82.

Hunter JE, Leslie M, Novak G et al. (2012) Depression and anxiety symptoms among women who carry the FMR1 premutation: impact of raising a child with fragile X syndrome is moderated by CRHR1 polymorphisms. *Am J Med Genet B Neuropsychiatr Genet* **159B**: 549–559.

Hunter JE, Rohr JK, Sherman SL (2010) Co-occurring diagnoses among FMR1 premutation allele carriers. *Clin Genet* **77**: 374–381.

Lovell B, Moss M, Wetherell M (2012) The psychosocial, endocrine and immune consequences of caring for a child with autism or ADHD. *Psychoneuroendocrinology* **37**: 534–542.

Movaghar A, Page D, Brilliant M et al. (2019) Data-driven phenotype discovery of FMR1 premutation carriers in a population-based sample. *Sci Adv* **5**: eaaw7195.

Nelson LM (2009) Clinical practice. Primary ovarian insufficiency. *N Engl J Med* **360**: 606–614.

North American Menopause Society (2012) The 2012 hormone therapy position statement of: The North American Menopause Society. *Menopause* **19**: 257–271.

Polussa J, Schneider A, Hagerman R (2014) Molecular advances leading to treatment implications for fragile X premutation carriers. *Brain Disord Ther* **3**. doi:10.4172/2168-975X.1000119.

Practice Committee of the American Society for Reproductive Medicine (2004) Current evaluation of amenorrhea. *Fertil Steril* **82**(Suppl 1): S33–339.

Practice Committee of the American Society for Reproductive Medicine (2004) Current evaluation of amenorrhea. *Fertil Steril* **82**: S33–S39.

Rebar RW (2009) Premature ovarian failure. *Obstet Gynecol* **113**: 1355–1363.

Roberts JE, Bailey Jr DB, Mankowski J et al. (2009) Mood and anxiety disorders in females with the FMR1 premutation. *Am J Med Genet B Neuropsychiatr Genet* **150b**: 130–139.

Rodriguez-Revenga L, Madrigal I, Alegret M, Santos M, Mila M (2008) Evidence of depressive symptoms in fragile-X syndrome premutated females. *Psychiatr Genet* **18**: 153–155.

Rohr J, Allen EG, Charen K et al. (2008) Anti-Mullerian hormone indicates early ovarian decline in fragile X mental retardation (FMR1) premutation carriers: a preliminary study. *Hum Reprod* **23**: 1220–1225.

Rossouw JE, Anderson GL, Prentice RL et al. (2002) Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *Jama* **288**: 321–333.

Sarimski K (1997) Behavioural phenotypes and family stress in three mental retardation syndromes. *Eur Child Adolesc Psychiatry* **6**: 26–31.

Schneider A, Johnston C, Tassone F et al. (2016) Broad autism spectrum and obsessive-compulsive symptoms in adults with the fragile X premutation. *Clin Neuropsychol* **30**: 929–943.

Seltzer MM, Barker ET, Greenberg JS, Hong J, Coe C, Almeida D (2012) Differential sensitivity to life stress in FMR1 premutation carrier mothers of children with fragile X syndrome. *Health Psychol* **31**: 612–622.

Seltzer MM, Greenberg JS, Hong J et al. (2010) Maternal cortisol levels and behavior problems in adolescents and adults with ASD. *J Autism Dev Disord* **40**: 457–469.

Sherman SL (2000) Premature ovarian failure in the fragile X syndrome. *Am J Med Genet* **97**: 189–194.

Smith LE, Hong J, Seltzer MM, Greenberg JS, Almeida DM, Bishop SL (2010) Daily experiences among mothers of adolescents and adults with autism spectrum disorder. *J Autism Dev Disord* **40**: 167–178.

Spath MA, Feuth TB, Allen EG et al. (2011) Intra-individual stability over time of standardized anti-Mullerian hormone in FMR1 premutation carriers. *Hum Reprod* **26**: 2185–2191.

Sullivan AK, Marcus M, Epstein MP et al. (2005) Association of FMR1 repeat size with ovarian dysfunction. *Hum Reprod* **20**: 402–412.